1.01
Aziridines and Azirines: Monocyclic

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1.01.1 Introduction – Monocyclic Aziridines

The aziridine functionality, occasionally referred to as an azaethylene or ethylenimine unit, is a valuable intermediate in organic chemistry <1994AGE599, B-2006MI1>. In terms of its synthetic behavior, its utility comes from selective ring-opening reactions <2004T2701, 2000S1347>. Transformations of this stable but strain-loaded (27 kcal mol^{-1}) three-membered ring allows for regio- and stereoselective installation of a wide range of functional groups in a 1,2-relationship to nitrogen. Cycloadditions of N-protected aziridines with various substrates occur to furnish complex heterocyclic systems. Aziridines are useful intermediates in natural product synthesis as in the case of the kainoids, (−)-mesembrine, (−)-platynesine, sphingosines, actinomycin, (±)-epicapreomycidine, and feldamycin. The aziridine functionality is also present in a small number of naturally occurring molecules. The biological properties of aziridine-containing compounds such as azinomycins, mitomycins, FR-900482, ficellomycin, miraziridine, maduropeptin, and azicemicins are of significant interest. The antibiotic and antitumor properties of several of these compounds are well known. It is impossible to comprehensively cover all of the numerous investigations dealing with monocyclic aziridines since 1995 in a chapter of this length. Consequently, only representative examples of aziridine reactivity and synthesis are highlighted. For further details, the reader is encouraged to consult the many review articles that have been published since the earlier CHEC-II(1996) review <1996CHEC-II(1A)1>.

1.01.2 Theoretical Methods

A number of the theoretical issues dealing with monocyclic aziridines were discussed in CHEC-II(1996) and CHEC(1984) <1996CHEC-II(1A)1, 1984CHEC(7)47>.

1.01.3 Experimental Structural Methods

Spectroscopic studies using X-ray, nuclear magnetic resonance (NMR), electron diffraction, microwave, and photoelectron methods have been used to determine the geometry and configurational stability of the monocyclic aziridine nitrogen atom <1996CHEC-II(1A)1>. These studies indicate that the barrier to pyramidal inversion of the nitrogen atom of aziridines is considerably higher than in acyclic amines, making it the dominant stereodynamic process for these heterocycles. The barrier for pyramidal inversion in aziridine itself is 19.5 kcal mol^{-1}. Aziridines are less basic than acyclic amines due to the increased s character of the nitrogen lone pair. The conjugate acid of aziridine has a pK_a value of 7.98, compared to a typical pK_a value of ca. 11 for the conjugate acid of an acyclic secondary amine <1996CHEC-II(1A)1>. The structural properties of aziridines, including spectroscopic features (NMR, mass spectrometry (MS), ultraviolet (UV), and infrared (IR)) were discussed in detail in CHEC-II(1996) and CHEC(1984) <1996CHEC-II(1A)1, 1984CHEC(7)47>.

1.01.4 Thermodynamic Aspects

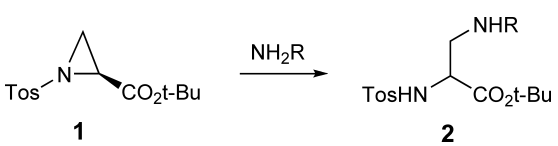
The ring-strain energy of aziridine is similar to that of cyclopropane (27 kcal mol^{-1}), reflecting high bond-angle strain <1996CHEC-II(1A)1>. Many of the reactions that aziridines undergo involve a nucleophilic opening of the three-membered ring and thus a release of strain energy. The lowering of the energy of activation in these strain-releasing reactions has been suggested not to be solely due to the release of strain. For further theoretical discussion of this issue, the reader is directed to Chapter 00102.

1.01.5 Reactivity of Monocyclic Aziridines

Aziridines have attracted considerable attention as starting materials in numerous applications, and many papers and review articles dealing with the synthesis of aziridines <1994AGE599> as well as their use in synthetic applications have been published since 1995 <2004T2701, 2000S1347, 2002CSR247, 2004PRC220>. In ring-opening reactions, it is common either to perform the reactions employing Lewis acid catalysis <1996H(43)2473, 2001J(P1)1314> or to activate the aziridine by substitution on the nitrogen <2004T2701>, thus increasing the ability of the nitrogen atom to function as a leaving group. It has been shown by Stamm <1999JPR319> that in order to carry out the reaction on nonactivated aziridines and in the absence of a catalyst, it is imperative that the nucleophile supplies a proton in order to create a neutral leaving group. Aziridines are well-known carbon electrophiles capable of undergoing reactions with various nucleophiles; this ability of undergoing regioselective ring-opening reactions contributes largely to their synthetic value. They are useful precursors for the synthesis of many biologically interesting molecules such as amino acids <1994AGE599, 2000S1347>, heterocycles <1992T6079>, and alkaloids <1990JOC46837>. As a consequence, many methods have been reported for the regioselective ring opening of aziridines with nucleophiles such as organometallic reagents <1993SL676>, silyl nucleophiles <2000JOC1344>, Wittig reagents <1993TL7421>, amines <1994TL7395>, halides <1998TL2385>, and alkenes <2000AGE4615>.

1.01.5.1 Nucleophilic Ring-Opening Reactions

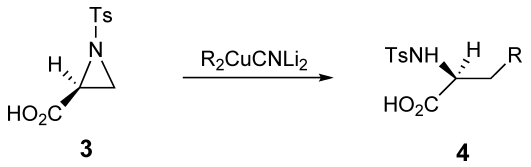
Similar to the epoxides, the most frequently encountered synthetic transformation for aziridines is nucleophilic ring opening, whereby heteroatom- and carbon-based nucleophiles are comparably important. The marked reactivity of aziridines toward ring opening and expansion relates to their extremely strained ring structures. There is, of course, no paucity of examples using heteroatom-based nucleophiles. For example, aziridine-2-*t*-butyl carboxylate **1** reacts with primary amines to give the dialkylated diamino-propionic acid derivatives **2**, which are interesting precursors for the synthesis of cyclosporin analogs. Attack occurs overwhelmingly at the least-hindered β-carbon (**Scheme 1**) <1995TL4955>.



1 **2**

Scheme 1

As an example of a ring opening using a carbon-based nucleophile, aziridine-2-carboxylate **3** can be ring-opened with higher-order cuprates to give the protected amino acid derivatives **4**, corresponding to attack at the less-substituted aziridine carbon (**Scheme 2**) <1995TL151>.

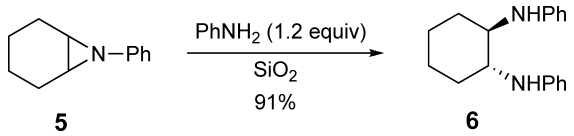


3 **4**

Scheme 2

1.01.5.1.1 Ring-opening reactions by amines

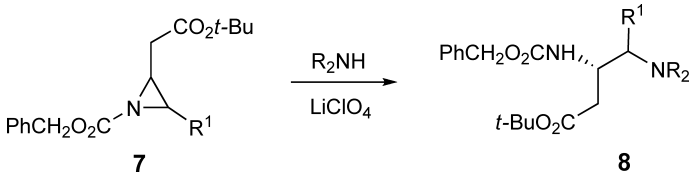
Amines are probably the most frequently encountered nucleophiles in this type of reaction. A recent report described the ring opening of aziridines using silica gel under solvent-free conditions. Thus, aziridine **5** was combined with a slight excess of aniline in the presence of silica gel to give the diaminocyclohexane **6** in 91% yield (**Scheme 3**) <2002TL3975>.



5 **6**

Scheme 3

Benzyloxycarbamate-protected aziridines such as **7**, although less activated than tosylaziridines, are sufficiently reactive to be easily and regioselectively opened by N-nucleophiles producing 1,2-diamino compounds **8** suitably protected for further transformations. The opening of aziridine **7** with the methyl ester of H-Lys(BOC)-OMe provided the methyleneaminopseudopeptide with a good yield and excellent regioselectivity, thereby affording a new route to this kind of compound (BOC = *t*-butoxycarbonyl, **Scheme 4**) <2006T3509>.

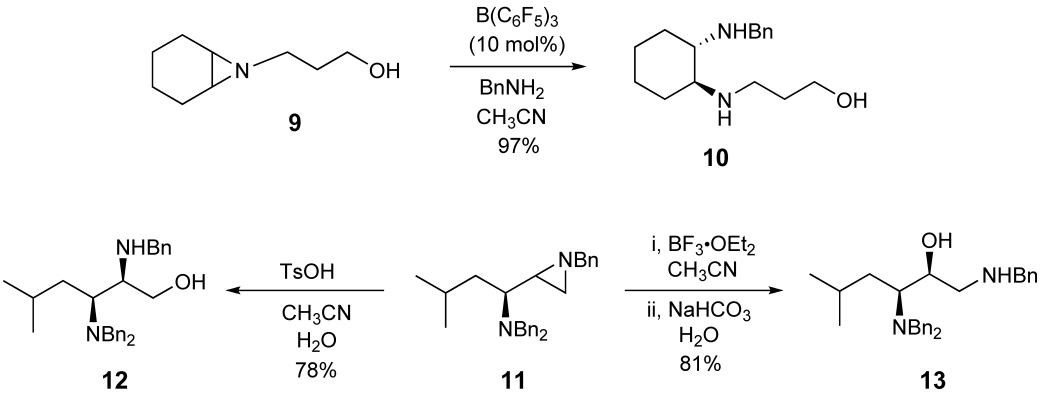


7 **8**

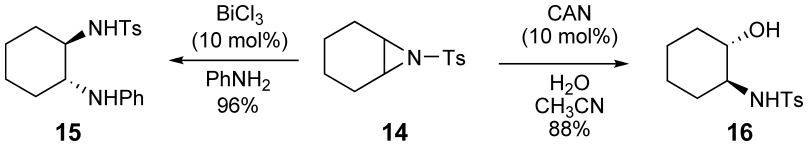
Scheme 4

Nonactivated aziridines can be prompted to undergo ring-opening reactions under the influence of tris(pentafluorophenyl)borane as a catalyst, as shown by the reaction of hydroxypropylaziridine **9** with benzylamine to give the diaminoalcohol **10**. Mechanistic studies suggest the intermediacy of $[(C_6F_5)_3B(H_2O)]\cdot H_2O$ formed *in situ* as a Brønsted acid catalyst <2003JOC5160>. In the case of amino aziridines **11**, the regioselectivity of the nucleophilic attack can be controlled by the reaction conditions. Thus, the use of a protic acid, such as *p*-toluenesulfonic acid (*p*-TsOH), leads to the attack of water at the less-hindered C-3 position, whereas the aprotic Lewis acid catalyst boron trifluoride etherate leads to a C-2 mode of ring opening. Anchimeric assistance from the amino substituent has been invoked as a rationale for the regiochemical changeover (**Scheme 5**) <2003JOC6407>.

Similarly, the *N*-tosylaziridine **14** is smoothly cleaved by aniline in the presence of bismuth trichloride acting as the Lewis acid to give the diamine **15** <2003SC547>. Ceric ammonium nitrate (CAN) catalyzes the ring opening of **14** with water to afford the amino alcohol **16** in 88% yield (**Scheme 6**) <2003CL82>.

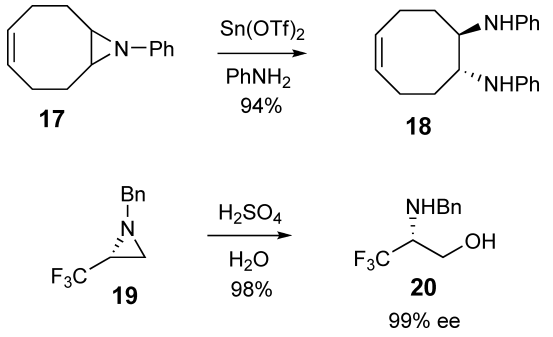


Scheme 5



Scheme 6

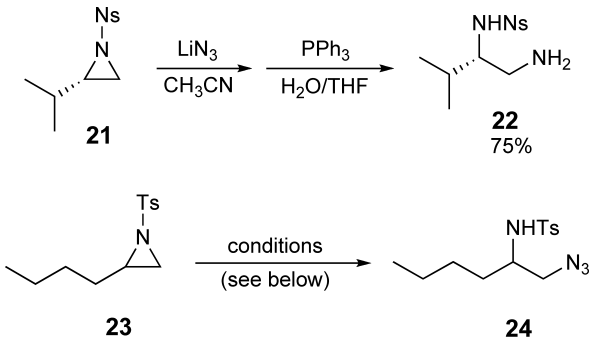
The bicyclic aziridine **17** was found to undergo smooth ring cleavage by aniline in the presence of $Sn(OTf)_2$ to give the corresponding 1,2-diamino compound **18** <1999JOC2537>. The chiral trifluoromethyl aziridine of type **19** can be ring-opened even with relatively weak nucleophiles (in this example, water) to give optically active amines **20** in good yields with excellent retention of configuration (**Scheme 7**) <1999JOC7323>.



Scheme 7

1.01.5.1.2 Ring-opening reactions by azides

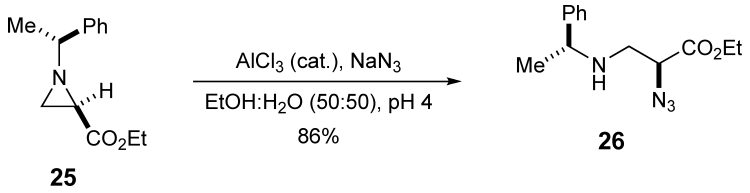
For the simplest amine nucleophile, the azide anion is often used in preference to ammonia, since the course of the reaction is more controllable. For example, the valinol-derived nosyl aziridine **21** was converted to the primary amine **22** by treatment with lithium azide followed by triphenylphosphine <2002OL949>. Sometimes azidolysis is sluggish and accompanied by unwanted isomerization reactions, so catalytic methods continue to be of interest. Along these lines, cerium(III) chloride promotes the regioselective ring opening of unsymmetrical tosyl aziridines at the terminal carbon, as exemplified by the conversion of alkyl aziridine **23** to azido amine **24** in 90% yield <2002OL343>. Indium trichloride catalyzes the analogous reaction using the somewhat milder reagent trimethylsilyl azide ($TMSN_3$) (**Scheme 8**) <2002SC1797>.



Nu	*Cat.*	*Yield (%)*	*Reference*
NaN_3	$CeCl_3$	90%	2002OL343
$TMSN_3$	$InCl_3$	85%	2002SC1797

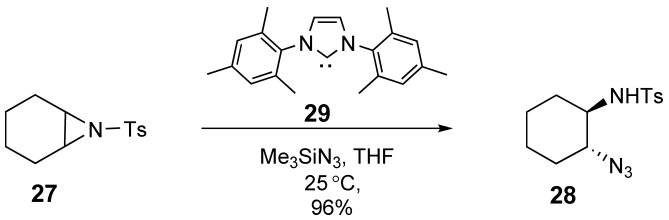
Scheme 8

The use of $AlCl_3$ to catalyze the ring opening of aziridine **25** by NaN_3 has proven surprisingly effective <2005TL4407>. The authors report complete inversion at the carbon bearing the azide to give the ring-opened azide **26**. Given the acidic reaction conditions, it is also interesting to note that the reaction was carried out on a several hundred gram scale without any difficulties (**Scheme 9**).



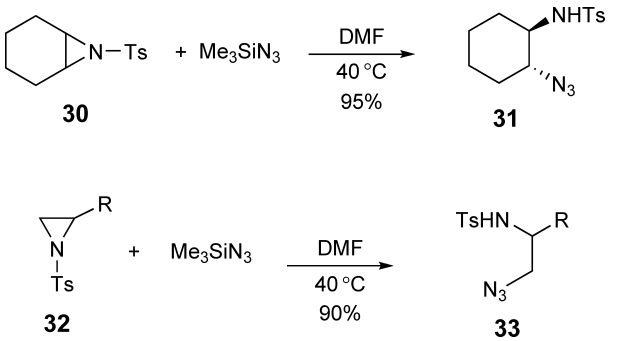
Scheme 9

Small organic molecules such as phosphines, amines, and nitriles have been utilized as catalysts to effect ring-opening reactions of aziridines. Recently, Wu *et al.* described the use of an N-heterocyclic carbene as an efficient catalyst in the ring-opening reaction of aziridines with trimethylsilyl (TMS) azide under mild reaction conditions. The advantages of this method include: (1) employing easily available N-heterocyclic carbene as the catalyst, (2) experimental ease of operation, (3) mild conditions, and (4) good substrate generality. A typical example involves the conversion of aziridine **27** into **28** at room temperature and in 96% yield using the N-heterocyclic carbene **29** (**Scheme 10**) <2006TL4813>.



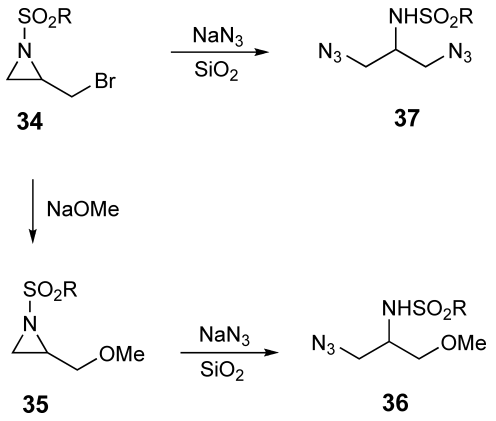
Scheme 10

Many ring-opening reactions of aziridines make use of silylated nucleophiles <2000JOC1344>. The reactions of aziridines can be carried out with silylated nucleophiles and without any catalysts under neutral conditions and proceed with high efficiency to furnish a variety of 1,2-bifunctional compounds such as **31** and **33** (**Scheme 11**) <2005EJO4769>.



Scheme 11

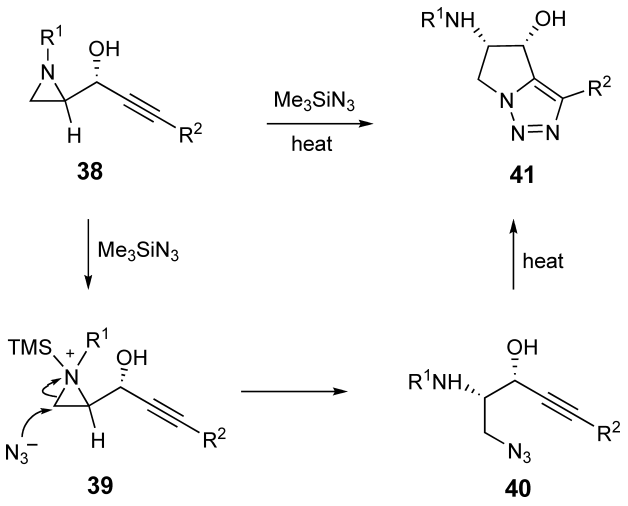
The versatility of 2-(bromomethyl)-1-sulfonyl-aziridines **34** as substrates in organic synthesis was demonstrated by allowing these substrates to react with water in the presence of silica gel to give 1,3-heteroatom-substituted 2-aminopropane derivatives. Monoazido **36** and diazidopropane derivatives **37** were prepared using sodium azide in water, as well as 1,3-diaryloxypropane sulfonamides using different potassium phenoxides as reagents. Since many methods are available for N-detosylation of sulfonamides, the methodology offers ready access to the synthesis of the corresponding amines (**Scheme 12**) <2005T8746>.



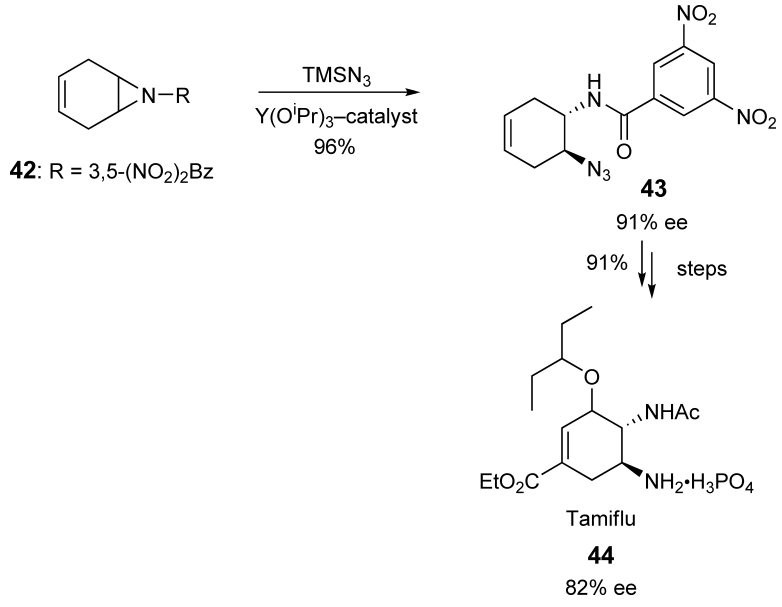
Scheme 12

Treatment of 1-aziridine-2-yl-propargylic alcohols **38** with trimethylsilyl azide followed by aqueous workup afforded azido amino alcohols of type **40**. The reaction was suggested to proceed via an activated aziridinium ion species **39** which is produced by the silylation of the aziridine nitrogen. A subsequent regioselective ring-opening reaction occurred by cleavage of the C(3)–N bond by the azide anion that was liberated from the trimethylazide reagents. Further heating of the azidoamino alcohol **40** gave the corresponding bicyclic triazoles **41** by an intramolecular 1,3-dipolar cycloaddition between the azide group and the adjacent alkyne (**Scheme 13**) <2005SL2187>.

Recently, an asymmetric synthesis of Tamiflu **44**, an orally active anti-influenza drug, was carried out by Shibasaki and co-workers utilizing a general catalytic enantioselective ring opening of *meso*-aziridine **42** with $TMSN_3$ in the presence of a Lewis-acidic yttrium catalyst <2006JA6312>. The enantiomerically enriched amidoazide **43** was obtained in 96% yield and 91% ee. This compound was subsequently converted to Tamiflu **44** using standard synthetic manipulations (**Scheme 14**).

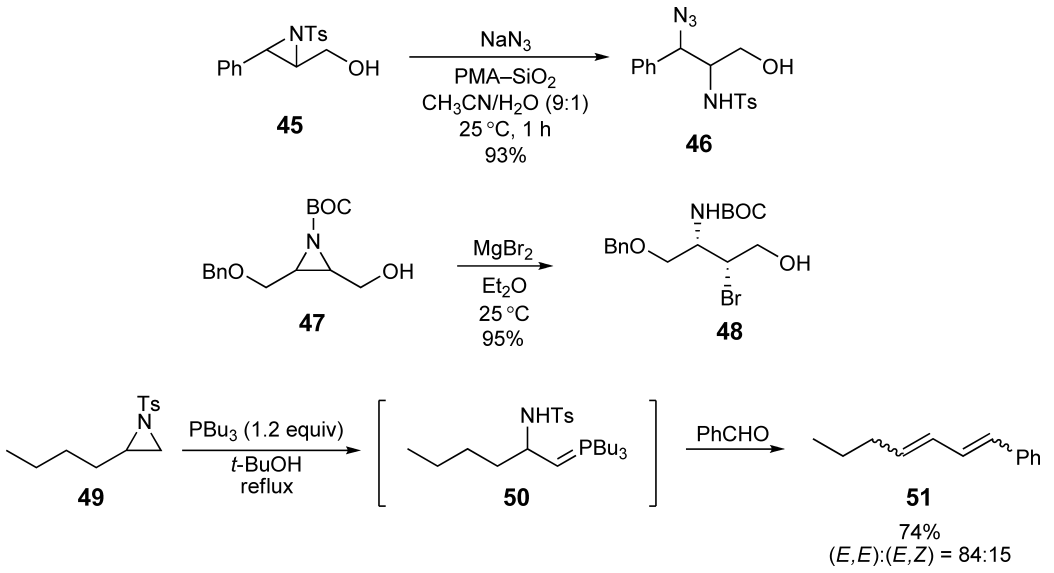


Scheme 13



Scheme 14

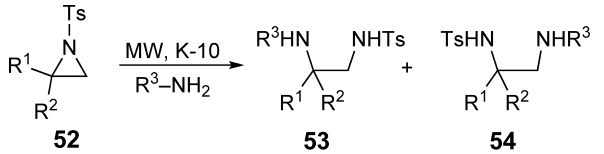
Silica-supported phosphomolybdic acid (PMA–SiO_2) has been found to be effective in promoting the ring cleavage of tosyl aziridines by a variety of nucleophiles. Thus, the azide anion preferentially attacks the benzylic position to provide the azidoaminoalcohol **46**, and the regioselectivity can be rationalized in terms of partial positive charge stabilization <2004SL1719>. A different type of selectivity is observed in the magnesium bromide-mediated opening of hydroxymethyl aziridines. In these systems, the delivery of the nucleophile (i.e., bromide) is under chelation control, as demonstrated in the conversion of aziridine **47** to the bromo aminoalcohol **48** <2004SC85>. In the absence of Lewis acid catalysts, heteroatomic nucleophiles tend to attack at the sterically least hindered center. Such is the case when the butylaziridine **49** is treated with tributylphosphine, a strong nonbasic nucleophile which smoothly opens the heterocyclic ring. The initial adduct undergoes rapid proton transfer to provide a betaine (**50**) which can serve as a Wittig reagent. The addition of benzaldehyde leads to an olefination/elimination sequence to afford the diene **51** as a mixture of (*E*/*Z*)-isomers (**Scheme 15**) <2004JOC689>.



Scheme 15

1.01.5.1.3 Ring-opening reactions by other N-nucleophiles

1,2-Diamines are another highly useful class of molecules with potent biological activity and are used as synthetic intermediates and as metal ligands. The ring-opening reactions of aziridines with amines and azide provides a facile route for the synthesis of 1,2-diamines. The use of microwave-induced Montmorillonite K-10 clay-catalyzed opening of tosyl aziridines provides an environmentally friendly route to 1,2-diamines **53** and **54** <2005TL2083>. In general, these ring-opening reactions are regioselective with both arylamines and aliphatic amines participating equally well. Particularly interesting is the opening of aziridine **52** ($R^1 = Me$, $R^2 = CO_2Me$) at the most-substituted carbon to provide diamino ester **53** (**Scheme 16**).



R^1	R^2	R^3	*Yield* (%)	*Ratio* (**53**:**54**)
H	Me	Ph	97	Only **54**
H	Me	$PhCH_2$	93	10:90
H	Ph	$PhCH_2$	92	90:10
Me	CO_2Me	Ph	85	Only **53**

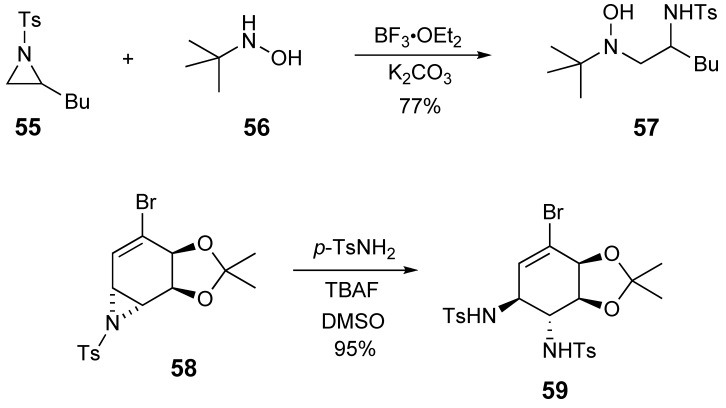
Scheme 16

Hydroxylamines also react with nonsymmetrical aziridines under Lewis-acidic conditions to give products of nucleophilic attack at the less-substituted site. Thus, treatment of methyl aziridine **55** with *N*-*t*-butylhydroxylamine **56** and 20 mol% boron trifluoride etherate provides the diamine derivative **57** in 77% yield <2001TL8243>. Fluoride ion is a powerful catalyst for the reaction of aziridines with the weakly nucleophilic *p*-toluenesulfonamide, a phenomenon which has been applied with advantage toward the preparation of protected diamino diol **59**, a precursor to the aminocyclitol substructure (**Scheme 17**) <2001TL6433>.

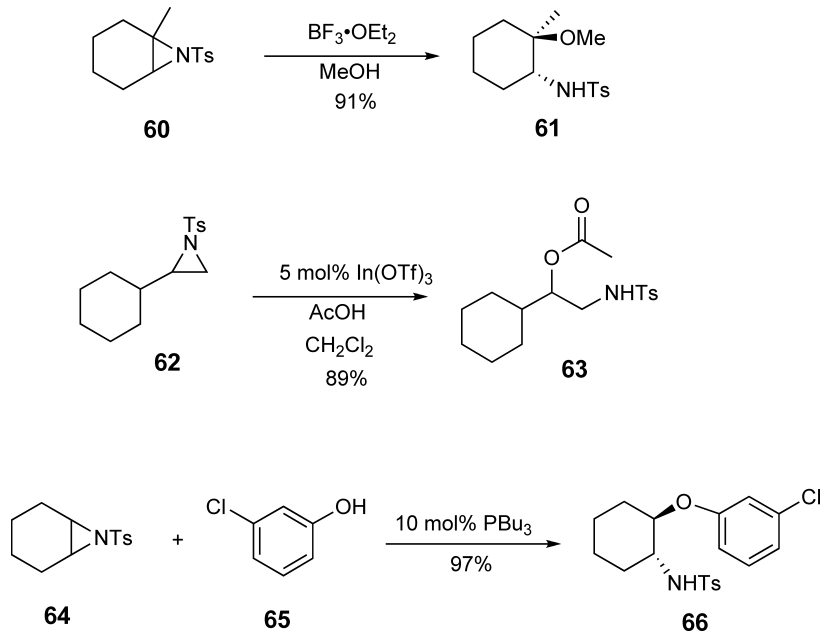
1.01.5.1.4 Ring-opening reactions by oxygen nucleophiles

The ring-opening reaction can also be induced by attack of oxygen-centered nucleophiles, as demonstrated by the facile ring cleavage of the unsymmetrical bicyclic aziridine **60** with methanol in the presence of boron trifluoride etherate to give the product of attack at the more-substituted aziridine carbon <2002T7355>. Indium triflate

catalyzes the opening of aziridines with carboxylic acids. For example, reaction of the cyclohexyl tosyl aziridine **62** with acetic acid and 5 mol% indium triflate resulted in the formation of amino acetate **63** in 89% yield, with a small amount of the regioisomer resulting from attack at the less-substituted position <2002TL2099>. Phenol-based nucleophiles are also capable of this behavior, and adding tributylphosphine to the mix has been shown to facilitate the reaction. Thus, the cyclohexene aziridine **64** provided the corresponding aryl ether **66** in 97% isolated yield in the presence of *m*-chlorophenol **65** and tributylphosphine, but no reaction was observed in the absence of a phosphine additive (**Scheme 18**) <2002JOC5295>.



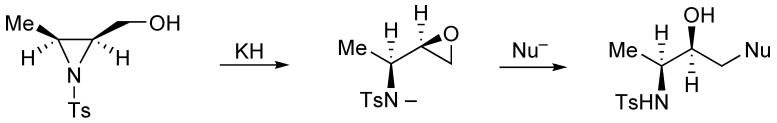
Scheme 17



Scheme 18

Hydroxymethylaziridine **67** undergoes ring opening in the presence of either carbon- or heteroatom-based nucleophiles upon treatment with 2 equiv of potassium hydride to provide the *vic*-aminoalcohol derivative **69**. The key step of the reaction is considered to be an aza-Payne rearrangement of the deprotonated aziridine methanol to the

epoxide **68**, which then undergoes nucleophilic attack at the less-substituted oxirane carbon to give the observed product. The process is carried out in one pot, is amenable to various nucleophiles (e.g., thiols, TMS-cyanide, higher-order cuprates), and proceeds with very good de (**Scheme 19**) <1995TL6247, 1998CSR145>.

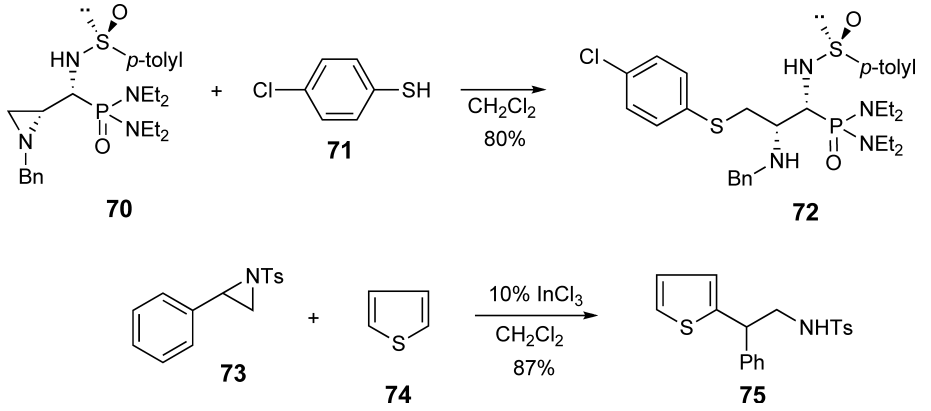


67 **68** **69**

Scheme 19

1.01.5.1.5 Ring-opening reactions by sulfur nucleophiles

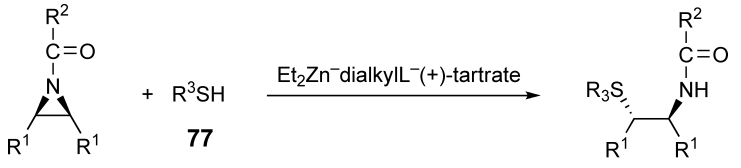
Sulfur-containing nucleophiles are equally suitable nucleophilic partners, as shown by the reaction of *p*-chlorophenol **71** with the functionalized sulfinylaziridine **70** to give the corresponding sulfide **72** in 80% yield <2002JOC2902>. Even thiophene **74** can attack the ring in the presence of indium trichloride. The regioselectivity of this reaction prefers the 2-position of the heterocycle and the benzylic site of the aziridine, although ca. 10% of product formation derives from terminal attack (**Scheme 20**) <2002TL1565>.



70 **71** **72** **73** **74** **75**

Scheme 20

Chiral dialkyl tartrate–diethylzinc complexes catalyze the asymmetric ring opening of symmetrical *N*-acylaziridines (e.g., **76**) with thiols to give thioamides (e.g., **78**) with up to 93% ee. The enantioselectivity is dependent upon the stoichiometry of the reactants and the nature of the tartrate (**Scheme 21**) <1996T7817>.

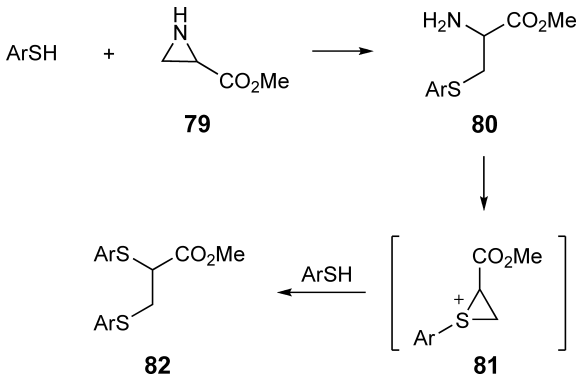


76 **77** **78**

Scheme 21

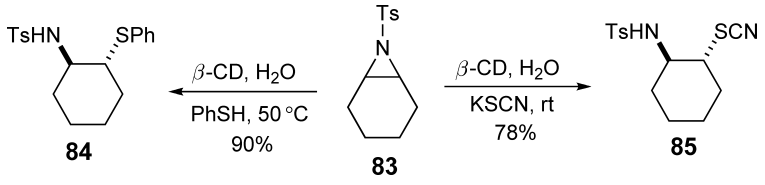
Interestingly, the ring opening of 2-aziridinecarboxylic acid methyl ester **79** by a number of aromatic thiols under solvent-free and noncatalytic conditions resulted in the formation of bis-arylsulfanyl propanoic acid esters **82**. Since only traces of the monosubstituted compound **80** were occasionally found in the crude reaction mixture, it would

appear that the product formed by initial attack by the thiol reacts much faster than the starting aziridine. This is probably due to anchimeric assistance from an intermediate episulfonium ion **81** (**Scheme 22**) <2006TL3949>.



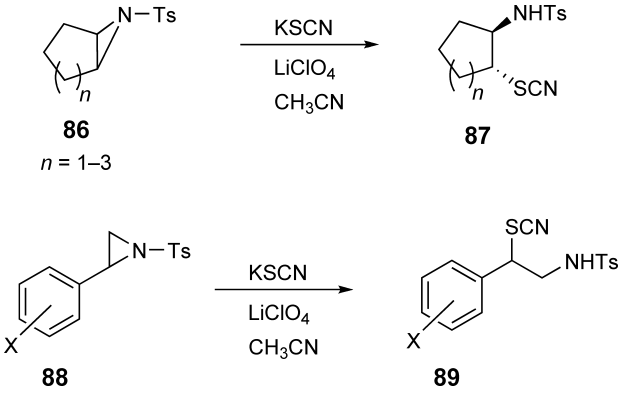
Scheme 22

β-Cyclodextrins (β-CDs) are very useful in creating microenvironments in which aziridines can be opened using mild conditions. The reaction of aziridines such as **83** with β-CD and sulfur nucleophiles such as thiocyanate <2005SL489> or thiophenols <2005TL6437> provides a mild route to ring-opened compounds **84** and **85** (**Scheme 23**).



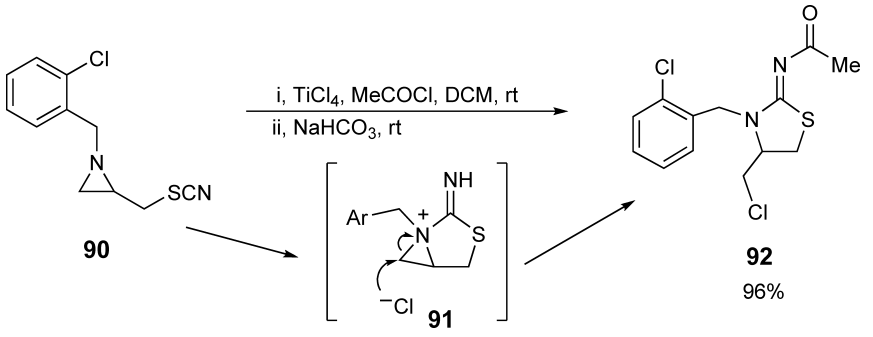
Scheme 23

Aziridines such as **86** react smoothly with potassium thiocyanate in the presence of a catalytic amount of lithium perchlorate in acetonitrile under mild reaction conditions to afford the corresponding β-aminothiocyanates **87** in high yields and with high regioselectivity. The combination of lithium perchlorate and acetonitrile provides a convenient catalytic medium to perform the reactions under neutral conditions (**Scheme 24**) <2005TL6385, 2006TL779>.



Scheme 24

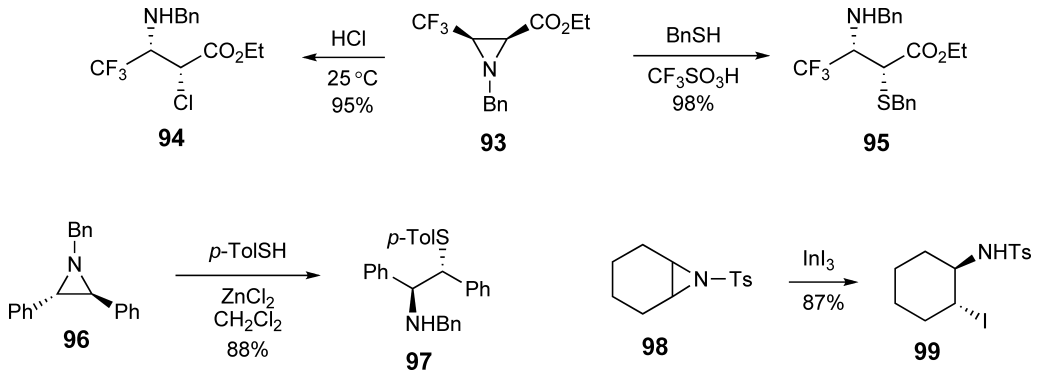
Several thiazolidines were synthesized via titanium tetrachloride catalytic cyclization <2005JOC227>. The reaction proceeds via an intramolecular attack on the nitrile by the aziridine nitrogen to provide bicyclic aziridinium intermediate **91**. Subsequent ring opening by chloride yields thiazolidine **92** (**Scheme 25**).



Scheme 25

1.01.5.1.6 Ring-opening reactions by halides and other nucleophiles

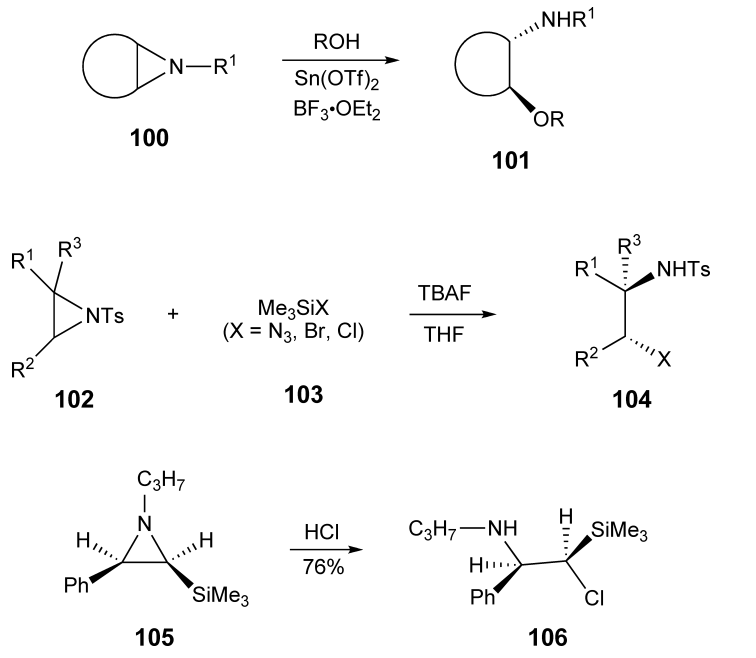
Aziridines engage in facile ring-opening reactions with many other types of nucleophiles, and this represents an entry into various functionalized amines. For example, the 3-trifluoromethylaziridine-2-carboxylate **93** undergoes efficient nucleophilic attack by chloride or thiols under acidic conditions to provide the protected amino esters **94** and **95**, respectively, in high yield and as a single diastereomer <2001SL679>. The latter reaction can also be promoted by zinc chloride, as exemplified by the conversion of aziridine **96** to amino sulfide **97** <2001(P1)1314>. As for halide-mediated ring opening, indium trihalides are competent reagents in promoting this transformation, as demonstrated by the clean conversion of *N*-tosyl aziridine **98** to the iodo amine derivative **99** (**Scheme 26**) <2001SL1417>.



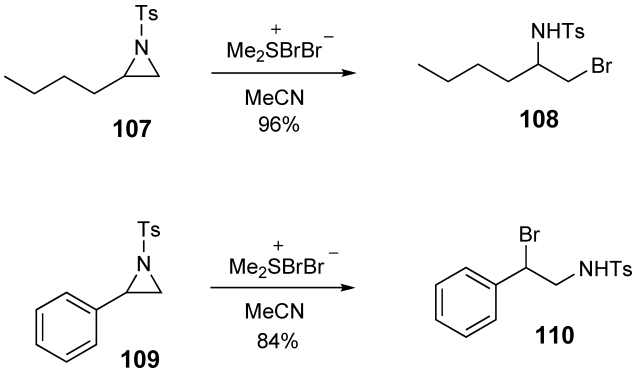
Scheme 26

A variety of N-activated aziridines **100** are efficiently cleaved by water, primary, allylic, and propargyl alcohols at room temperature in the presence of catalytic amounts of tin triflate and boron trifluoride etherate <2000TL4677>. Aziridines can also be ring-opened by trimethylsilyl compounds **103** and tetrabutylammonium fluoride to give cyano-, azido-, and chloramines in simple and efficient fashion <2000JOC1344>. Silyl-substituted aziridines **105** are attacked by hydrogen halides to furnish the corresponding haloamine compound **106** (**Scheme 27**) <2000J(P1)439>.

N-Tosylaziridines **107** and **109** undergo ring opening efficiently with (bromo-dimethyl)sulfonium bromide at room temperature to form the corresponding β-bromoamines **108** and **110**. The conversions are highly regioselective and furnish the products in excellent yields within a short period of time. The reaction uses an inexpensive reagent, is operationally simple, involves short reaction times, and proceeds in high yield and with excellent regioselectivity (**Scheme 28**) <2006TL4457>.

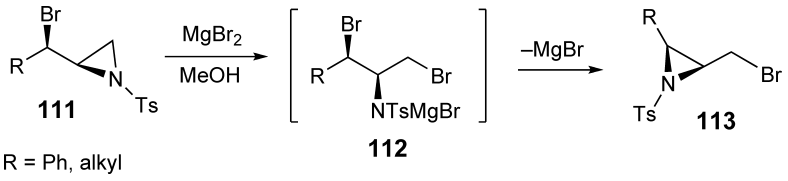


Scheme 27



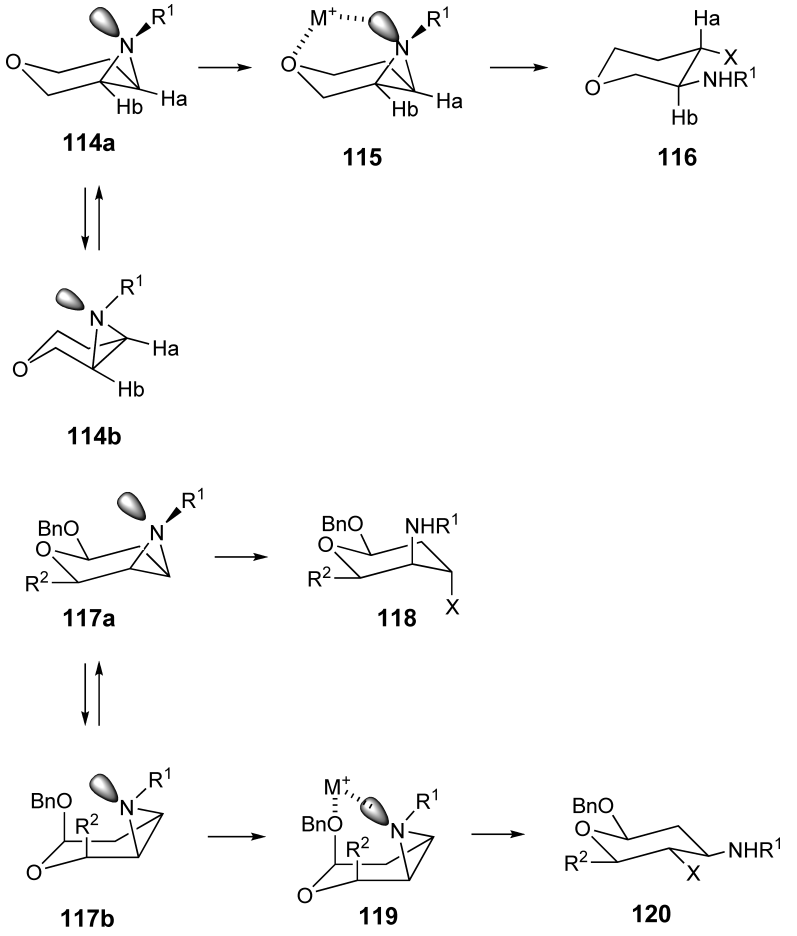
Scheme 28

A novel stereospecific isomerization of 2-(1-bromoalkyl)-1-sulfonylaziridines **111** into 2-(bromomethyl)-3-alkyl-1-sulfonylaziridines **113** was reported to occur by carrying out the reaction in the presence of $MgBr_2$. The isomerization reaction was found to be considerably dependent on the nature of the solvent used. Polar solvents such as MeOH or dimethylformamide (DMF) are able to solvate the magnesium bromide and give **113** as the thermodynamically most stable regioisomer (**Scheme 29**) <2005TL6541>.



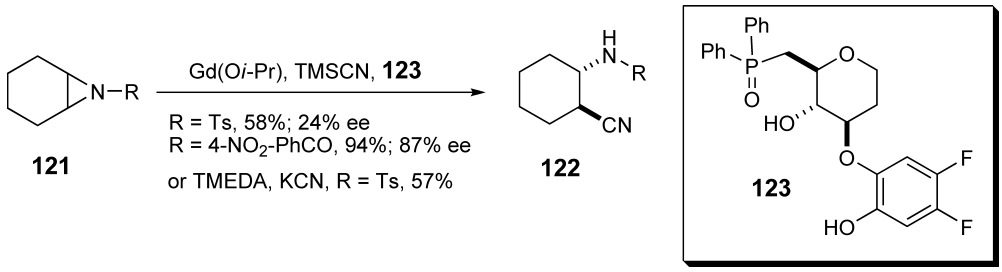
Scheme 29

Crotti *et al.* <1997T1417> have studied the ring-opening behavior of certain bicyclic aziridines under standard and chelating conditions; their findings are in keeping with those obtained from similar epoxide systems, namely that the course of the aziridine cleavage can be strongly influenced by the reaction conditions and the topography of the substrate. For example, when the two bicyclic aziridines **114** and **117** undergo nucleophilic attack under standard conditions, a strong C-1 preference is observed. In the former system, the C-2 position is believed to be deactivated toward nucleophilic attack due to the electronic effect of the pyransidic oxygen; in the latter, the observed selectivity is presumably due to the predominance of the more stable conformer **117a**, in which the benzylic group assumes an equatorial attitude. Introduction of a chelating metal into the reaction system causes an enhancement of C-1 selectivity in the case of **114**, yet a complete crossover is observed for the benzylic derivatives **117**. In both cases, the role of the metal is thought to be in the formation of a bidentate chelate structure (i.e., **115** and **119**) which further stabilizes the already low-energy intermediate **115** in the first series, but which coordinates with the benzylic oxygen in the latter case (i.e., **119**) to lock in an otherwise disfavored conformation, leading to C-2 products **120** (**Scheme 30**).



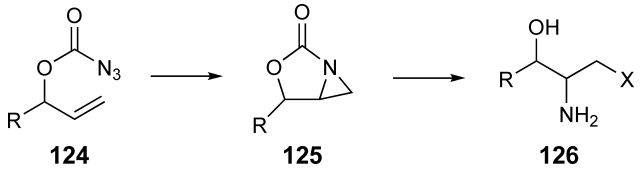
Scheme 30

The gadolinium•**123** complex was used to catalyze the enantioselective desymmetrization of an assortment of aziridines <2005JA11252>. The substitution on the nitrogen was critical to obtaining optimal yields and enantioselectivity. The use of *N*-tosyl aziridine gave **122** with only 24% ee while changing to the *p*-nitrobenzoyl gave **122** with an 87% ee. Aziridines have also been opened through the use of nucleophilic catalysis <2005OL3509>. Several nucleophilic catalysts were examined for the preparation of cyanoamides, **122**, and the optimal choice was tetramethylethylenediamine (TMEDA, 20 mol%). This represents a significant departure from the more typical acid catalysis used for aziridine ring opening (**Scheme 31**).



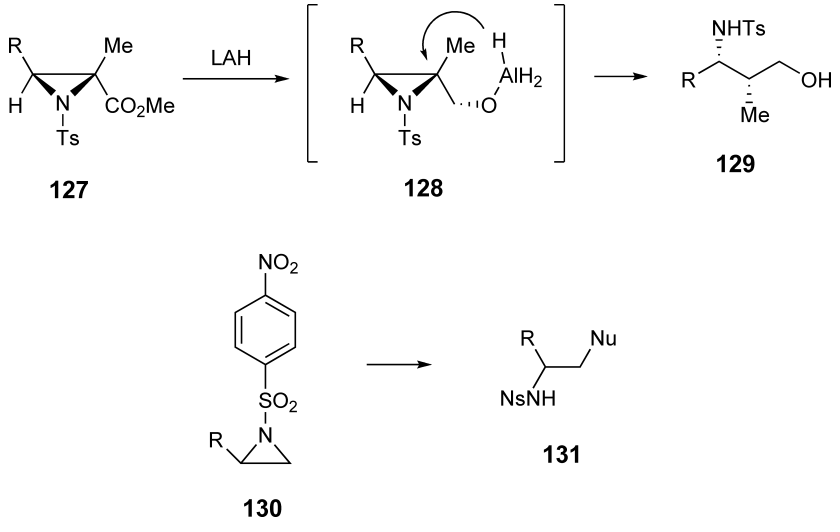
Scheme 31

The ring opening of a bicyclic aziridine is the key step in a novel synthesis of vicinal amino alcohols **126** from allylic alcohols. In this protocol, the thermolysis of an azidoformate **124** results in the formation of a nitrene which is captured intramolecularly to generate the strained bicyclic system **125**. The methylene carbon of the aziridine ring proved to be very susceptible to ring opening providing intermediate oxazolidinones, which on hydrolysis, yielded substituted amino alcohols (**Scheme 32**) <1997JOC4449>.



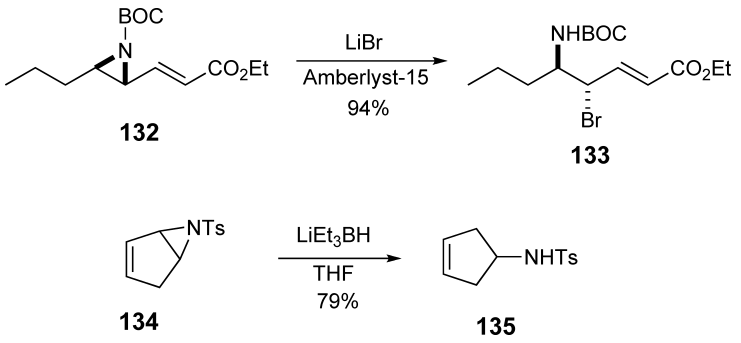
Scheme 32

The aziridine nucleus is frequently activated toward nucleophilic attack by attaching electron-withdrawing substituents to the nitrogen atom, as illustrated by the chiral *N*-tosylaziridine 2-carboxylate esters **127**, which undergo a highly stereoselective ring opening upon treatment with lithium aluminum hydride. In this case, the attack of hydride causes inversion of configuration and is directed by the hydroxyl group. This sequence is presented as an efficient asymmetric synthesis of α-alkyl-β-amino acids <1997TL5139>. In a similar vein, the *p*-nitrophenyl-sulfonyl (nosyl) group is also a useful activating group for ring-opening reactions. Nosyl aziridines **130** are highly reactive electrophiles toward a variety of nucleophiles and do not exhibit competing S_NAr reactivity; furthermore, the resultant nosylamide adducts **131** can be cleaved under mild conditions (**Scheme 33**) <1997TL5253>.



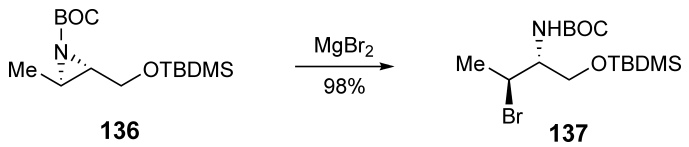
Scheme 33

Other useful nucleophiles for the ring opening of aziridines include bromide, as shown in the Amberlyst-15-catalyzed reaction of lithium bromide with vinyl aziridine **132** <2002TL5867> and hydride, which can be delivered by lithium triethylborohydride. This is illustrated by the conversion of tosyl azabicyclo[3.1.0]hexene **134** to the corresponding protected cyclopentenyl amine **135** in 79% yield (**Scheme 34**) <2002TL723>.



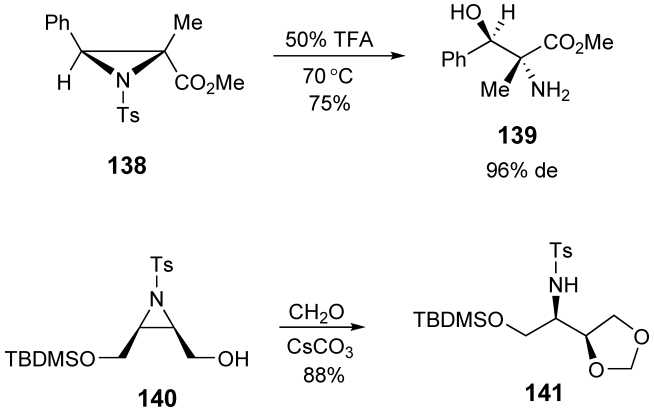
Scheme 34

N-BOC-2,3-aziridinoalcohol derivatives **136** undergo ring opening in a regio- and stereoselective fashion with magnesium bromide to give the corresponding 3-bromo-1,2-aminoalcohols **137**, thereby demonstrating a novel use of the BOC substituent as both a protecting and activating group. The products obtained can be deprotected under very mild conditions (**Scheme 35**) <1998TL2385>.



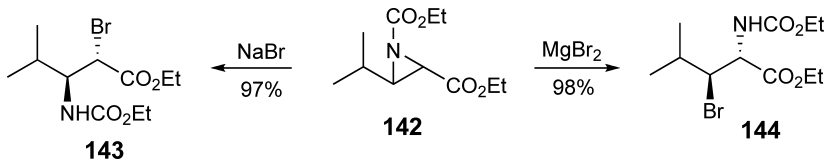
Scheme 35

If the starting aziridine is already optically pure, then it is desirable to preserve the ee during any subsequent ring openings. In this vein, 2-substituted aziridine **138** can be cleaved in a regio- and stereocontrolled manner upon heating to 70 °C in 50% trifluoroacetic acid (TFA) to give (2*R*,3*R*)-(+)-α-methyl-β-phenylserine **139** in 75% yield and 96% de <1996TL5473>. In an interesting intramolecular example of this process, aziridinylmethanol **140** reacts with formaldehyde in the presence of cesium carbonate to form a hemiacetal intermediate, which cyclizes with concomitant aziridine ring opening to furnish acetal **141**, which was then used to synthesize a key synthetic intermediate for bestatin (**Scheme 36**) <1996H(42)701>.



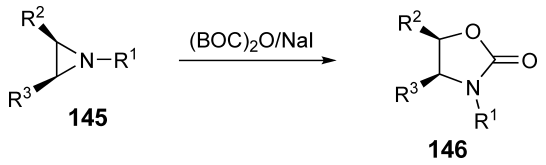
Scheme 36

The regioselectivity of such nucleophilic ring-opening reactions can sometimes be controlled by the reaction conditions. A striking example of such reaction steering is given by the cleavage of 3-substituted *N*-ethoxycarbonyl aziridine-2-carboxylates (e.g., **142**) with metal halides. Thus, treatment of **142** with sodium bromide leads to exclusive C-2 attack, providing amino acid derivative **143** as the sole product. On the other hand, use of magnesium bromide results in a complete crossover of reactivity to give isomer **144** via C-3 attack, presumably due to chelation effects (**Scheme 37**) <1996TL6893>.



Scheme 37

Certain reagents promote ring opening and subsequent cyclization to give other heterocycles. For example, di-*tert*-butyl dicarbonate induces the stereoselective ring transformation of *N*-alkyl aziridines **145** into oxazolidin-2-ones **146** (**Scheme 38**) <1996T2097>.



Scheme 38

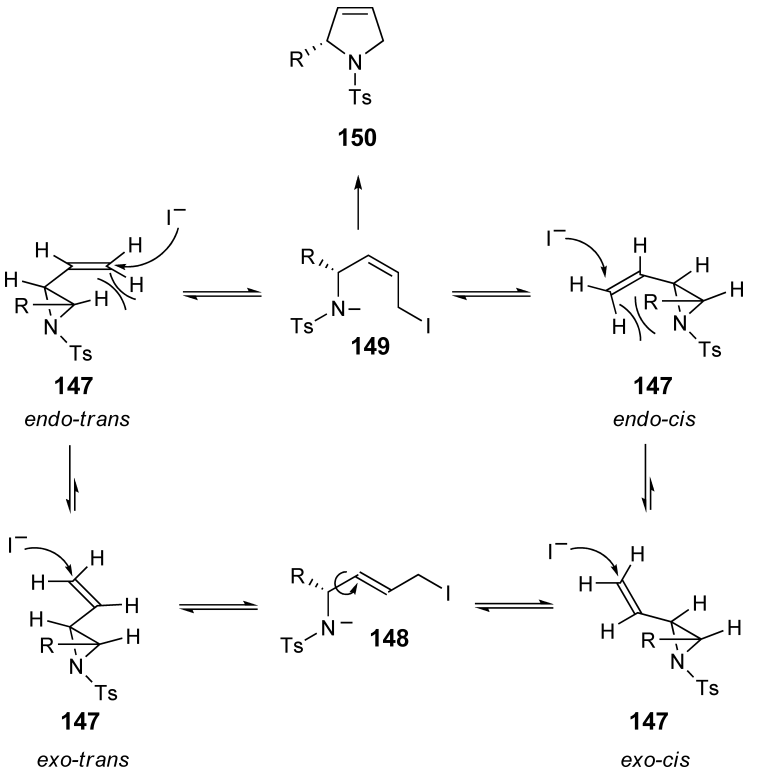
A convenient protocol for the formation of synthetically important 3-pyrrolines (i.e., **150**) involving a microwave-assisted rearrangement of 2-vinylaziridines **147** has been developed. The rearrangement proceeds in good to excellent yields and is mediated by NaI or LiI in MeCN at elevated temperatures. The proposed mechanism for the rearrangement starts with an S_N2' ring opening of *trans*-**147**. Opening in the *exo-trans*-**147** conformation leads to intermediate **148** with (*E*)-configuration, whereas the thermodynamically less favored *endo-trans*-**147** conformation will give the (*Z*)-configured intermediate **149**. Only the latter intermediate can ring-close to the desired pyrroline **150**. Intermediates **148** and **149** only result in the reformation of the aziridine moiety (**Scheme 39**) <2005SL3099>.

1.01.5.1.7 Ring-opening by carbon-centered nucleophiles

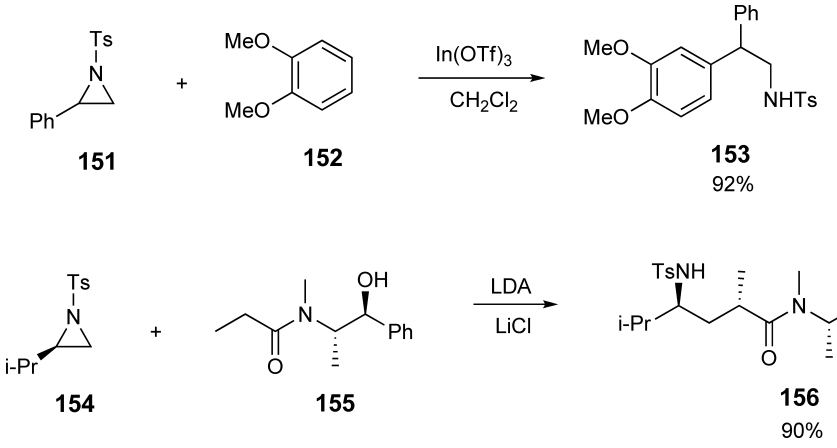
Some interesting advances have also been made in the area of ring opening by carbon-centered nucleophiles, an area of obvious practical impact. For example, aziridines react smoothly with arenes in the presence of a catalytic amount of indium triflate at ambient temperature to give the corresponding β-aryl amines (e.g., **153**) in good to excellent yields <2001TL8067>. The aziridine **154** was opened up in a stereocontrolled fashion by the chiral enolate prepared by deprotonation of **155**, itself derived from (*S*,*S*)-(+)-pseudoephedrine, and provides the γ-aminoamide **156** in 90% yield (**Scheme 40**) <2001JOC5801>.

Indole derivatives **157** also serve as carbon-centered nucleophiles in the scandium-mediated opening of aziridine carboxylates **158**. The overall process represents a facile synthesis of aryl-substituted tryptophans **159** (**Scheme 41**) <1998SL754>.

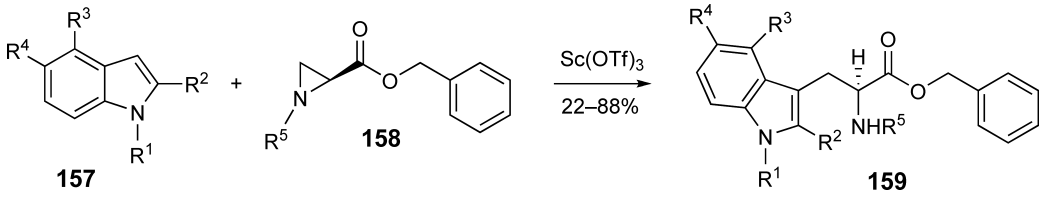
Alkynylation of aziridines can be effected through the copper-catalyzed ring opening with acetylides. For example, lithium phenylacetylide engages in smooth nucleophilic attack of *N*-tosyl-7-azabicyclo[4.1.0]heptane **160** in the presence of copper(I) triflate to provide the cyclohexyl alkyne **161** in excellent yield (**Scheme 42**) <2004SL1691>.



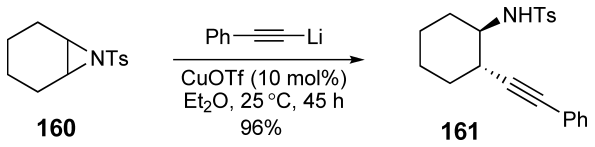
Scheme 39



Scheme 40

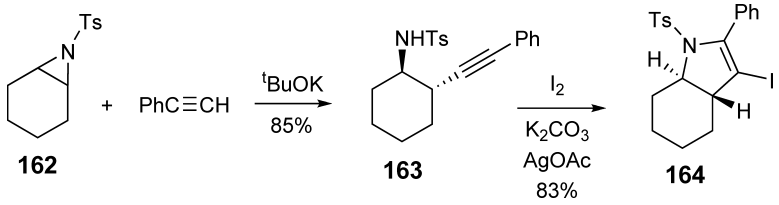


Scheme 41



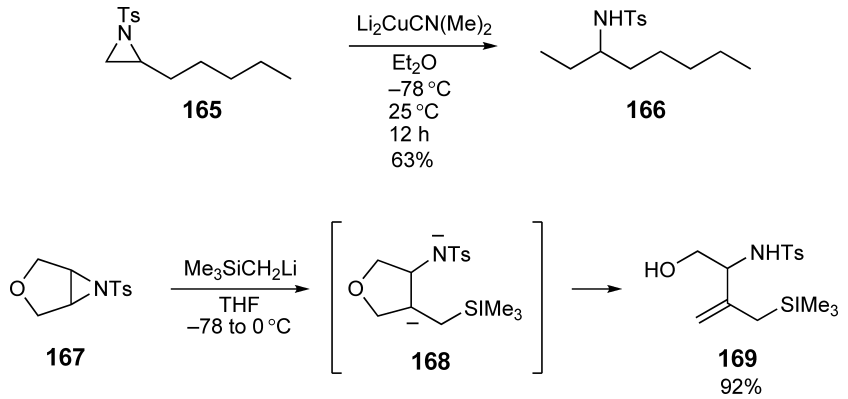
Scheme 42

In the presence of *t*-BuOK, the reaction of acetylenes with *N*-tosyl-substituted aziridines derived from both cyclic and acyclic alkenes at room temperature gave rise to homopropargylamines in high yield and high regioselectivity. Not only phenyl- and Me_3Si-substituted acetylenes but also acetylene itself were suitable reagents. Treatment of the ring-opening product **163** with I_2 and AgOAc in the presence of K_2CO_3 provided dihydropyrrole **164** in high yields (**Scheme 43**) <2005T9586>.



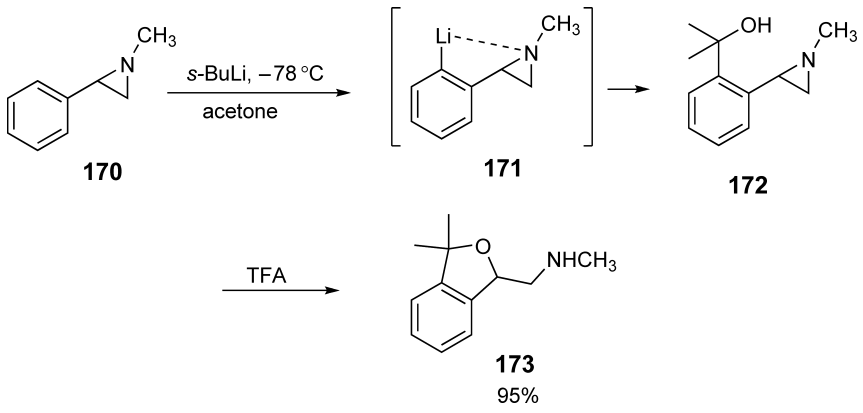
Scheme 43

Lithium dimethyl cyanocuprate can also be engaged in nucleophilic attack and this occurs on the less-substituted carbon with 1-pentyl-*N*-tosylaziridine **165** to give *N*-tosyloctane-3-amine **166**. In this system, the use of alkyllithium reagents led to eliminative pathways <2004T3637>. However, there are other reports of productive ring opening by lithiates. Treatment of 6-aza-3-oxabicyclo[3.1.0]hexane **167** with (trimethylsilyl)methyllithium led to the formation of an intermediate ring-opened dianion **168**, which subsequently underwent elimination to form the functionalized allylic amine **169** <2004CC2234>. Key to the success of this protocol is the formation of the aziridinyl anion, which has considerable carbenoid character (**Scheme 44**).



Scheme 44

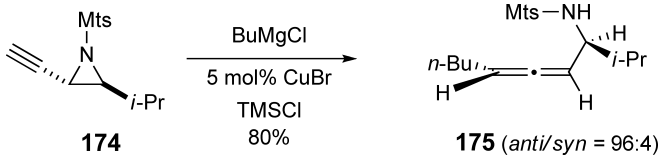
In a very clever reaction sequence, *N*-methylaziridines have been shown to be useful directing groups for *ortho*-metallation <2005OL3749>. Reaction of **170** with *s*-BuLi followed by trapping with a carbonyl compound provides alcohol **172**. Subsequent intramolecular aziridine ring opening provides isobenzofuran derivative **173** (**Scheme 45**).



170 **171** **172** **173** 95%

Scheme 45

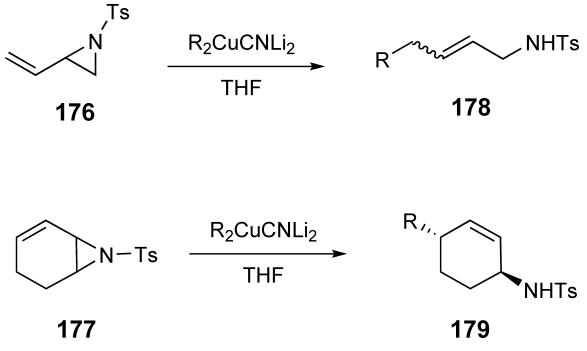
The synthetically important subclass of alkynyl aziridines was included in a relatively recent review <2002COR539>, specifically from the standpoint of preparation and ring-opening reactions with carbon nucleophiles. Such substrates (e.g., **174**) tend to suffer S_N2' attack from Grignard reagents to give aminoallenes (e.g., **175**) (**Scheme 46**).



174 **175** (*anti*/*syn* = 96:4)

Scheme 46

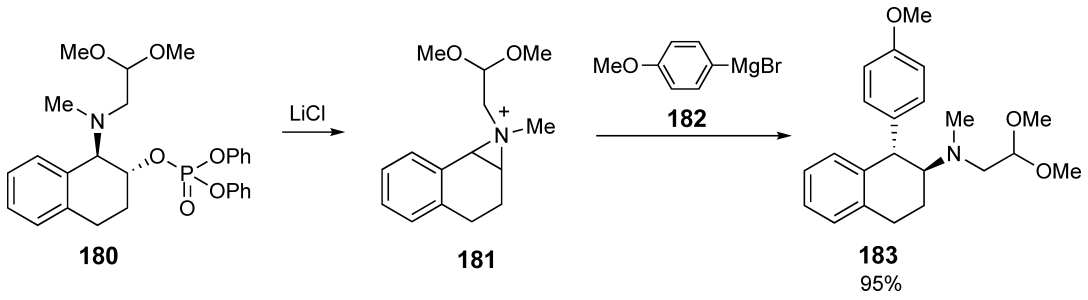
Two structurally simple 2-alkenyl aziridines corresponding to the acyclic **176** and cyclic **177** were treated with routinely used organometallic reagents. With these systems, the lithium or magnesium cyanocuprates reacted cleanly with **176** and gave **178** with very high S_N2' selectivity. The reaction of the cuprate with **177** was also S_N2'-regioselective, furnishing the *trans*-3,6-disubstituted cyclohexene **179** as the major product of the reaction (**Scheme 47**) <2005TL2539>.



176 **178** **177** **179**

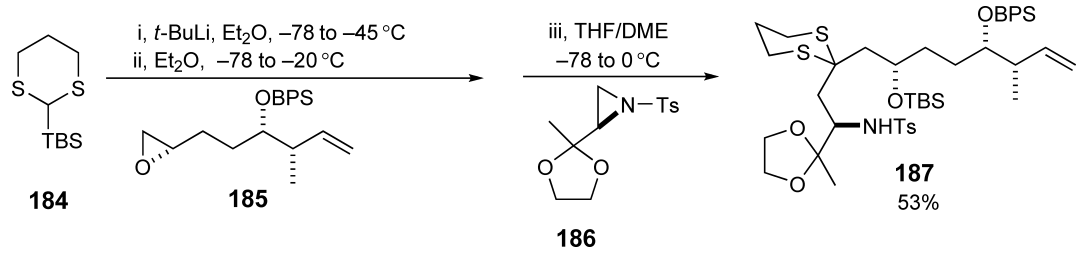
Scheme 47

An organometallic reagent has been used to ring-open an aziridinium ion **181**, formed *in situ* by the treatment of the amino alcohol derivative **180** with lithium chloride. Subsequent addition of the aryl magnesium bromide **182** led to the formation of amine **183** in 95% overall yield (**Scheme 48**) <2002TL6121>.



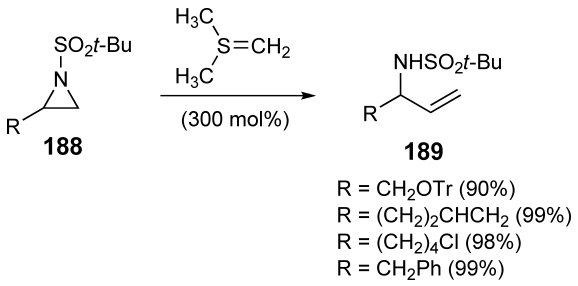
Scheme 48

In the synthesis of poison frog alkaloid (−)-205B, a three-component linchpin coupling was used to form a complex intermediate, **187**, in a single step <2005OL3247>. Lithiation of **184** followed by addition of epoxide **185**, warming, and then addition of aziridine in tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) to trigger the Brook rearrangement leads to **187**. This tactic, in conjunction with a one-flask sequential cyclization, constitutes an effective general strategy for the construction of indolizidine and related alkaloids (**Scheme 49**) <2006JOC2547>.



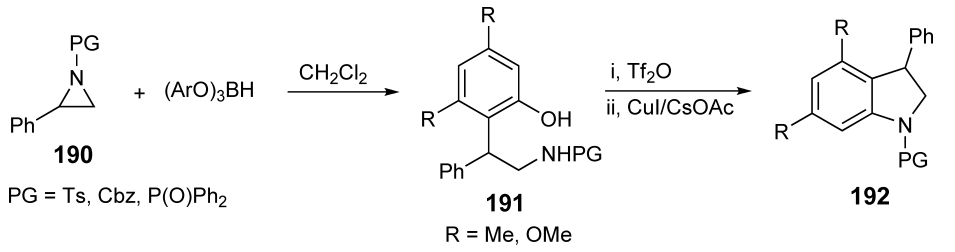
Scheme 49

The homologation of aziridines to give allylic amines is an attractive process to a very useful class of molecules. Thus, the reaction of N-protected aziridines with excess dimethylsulfonium methylide provides the homologated allylic amines in excellent yields (**Scheme 50**) <2005OL3295>.



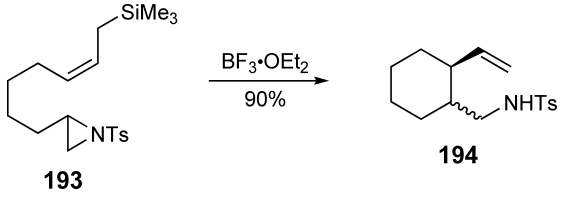
Scheme 50

A new carbon–carbon coupling reaction of phenol derivatives with aryl aziridines has been reported to occur with high regioselectivity and high *syn*-selectivity, without the need for any external transition metal catalyst or Lewis acids. Thus, reaction of electron-rich borates with optically active aziridines of type **190** in CH_2Cl_2 at −78 °C provided the unsymmetrical 2,2-diaryl ethylamines **191**, which can be further used to produce stereodefined substituted 3-aryl indolines <2006OL2627>. Conversion of the phenolic OH group to the corresponding triflate followed by a CuI/CsOAc-mediated intramolecular amination was the route used to synthesize the substituted 3-aryl indoline **192** (**Scheme 51**).



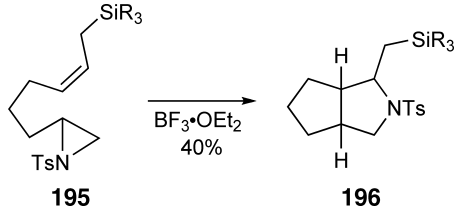
Scheme 51

The aziridine ring may also be opened in an electrophilic fashion using an intramolecular carbon nucleophile. For example, the aziridine nucleus of the functionalized allyl silane **193** undergoes intramolecular ring opening in the presence of boron trifluoride etherate to give the aminomethyl vinyl cyclohexane **194** in 90% yield as a 2.7:1 mixture of *cis*- and *trans*-isomers (**Scheme 52**) <1995TL3793>.



Scheme 52

When the related aziridine **195** was used containing one less carbon in the tether, an unusual cyclization occurred which corresponds to a formal [3+2] aziridine allylsilane cycloaddition to give the bicyclic pyrrolidine **196**. This substrate was used for the preparation of other fused ring systems (**Scheme 53**) <1999T8025>.



Scheme 53

1.01.5.2 Reactions of N-Unsubstituted Aziridines

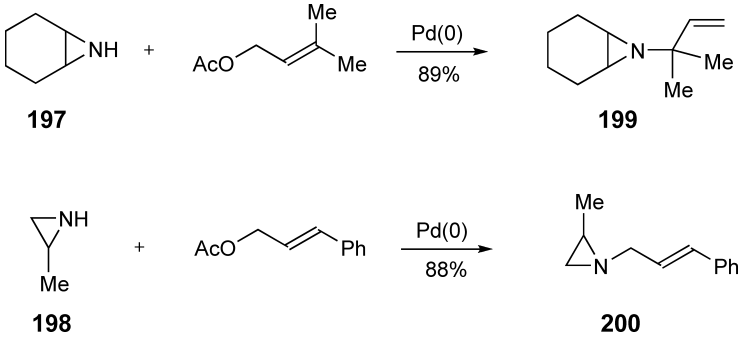
1.01.5.2.1 Palladium-catalyzed allylic amination

N-Allylation of aziridines is often complicated by side reactions. The classical solution to this problem, reductive amination, can also be problematic due to the increased strain energy of the aziridinium intermediate. A way to avoid this difficulty was developed by Yudin and co-workers <2005JA17516, 2004JA5086>. The results obtained showed that NH-aziridines such as **197** or **198** underwent a palladium-catalyzed allylic amination with various allyl acetates affording the desired allylated product **199** and **200** with high levels of regioselectivity and in high isolated yields (**Scheme 54**).

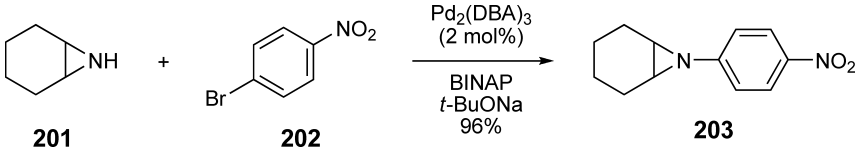
1.01.5.2.2 Palladium-catalyzed alkenylation and arylation

N-Unsubstituted aziridines can be elaborated by taking advantage of the nucleophilicity of the nitrogen center. One noteworthy example is the palladium-catalyzed arylation of aziridine **201** with *p*-bromonitrobenzene **202** using a

$Pd_2(DBA)_3$/BINAP system (DBA = dibenzylideneacetone; BINAP = 2,2-bis(diphenyl-phosphanyl)-1,1-binaphthyl). Best results were obtained using electron-deficient aryl bromides. Aryl chlorides of any type, however, failed to react under these conditions. The aryl–aziridine coupling reaction could also be carried out with arylboronic acids using a copper catalyst (**Scheme 55**) <2003JOC2045>.

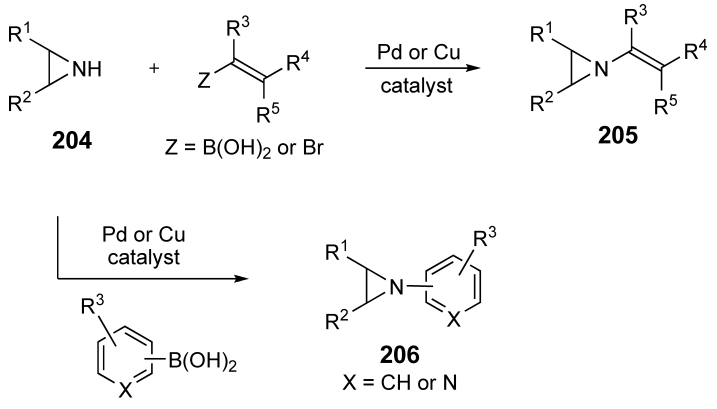


Scheme 54



Scheme 55

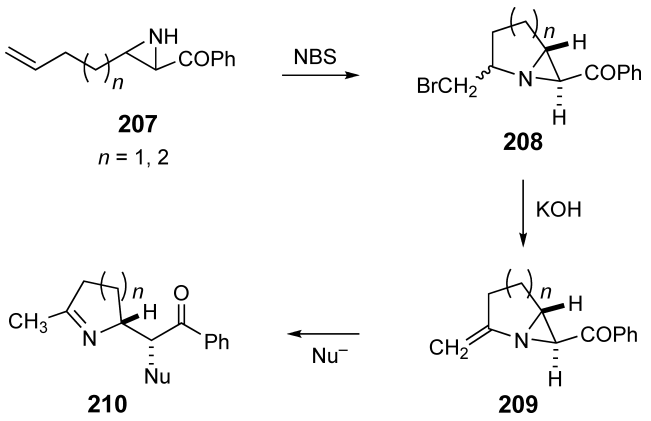
A range of *N*-aryl- and *N*-alkenylaziridines have been prepared by the palladium- or copper-catalyzed reaction between unsubstituted aziridines and aryl or alkenyl bromides or boronic acids without opening of the strained aziridine ring <2003JOC2045>. The $Pd_2(DBA)_3$/BINAP combination in toluene at 70 °C with *t*-BuONa as base serves as an effective catalyst for the amination of unsubstituted aziridines. Using this methodology, one can synthesize N-arylated products in 35–96% yield (**Scheme 56**). The insertion of palladium into the nitrogen carbon bond was not observed in any of these cases, although oxidative addition of Ni to *N*-tosylaziridines has been reported <2002JA2890> and oxidative addition of transition metals to aziridines has been invoked in catalytic carbonylation of aziridines to give *β*-lactams <1989JA931>.



Scheme 56

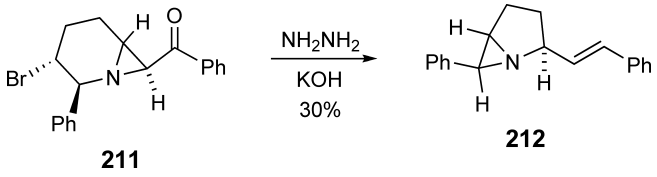
1.01.5.2.3 Intramolecular oxidative cycloamination

Synthetically versatile [3.1.0] and [4.1.0] bicyclic enamines have been prepared by intramolecular oxidative cycloamination of N-unsubstituted aziridine-containing tethered alkenes <2006JOC6067, 2006ACR194, 2003JA14242>. This process is initiated by *N*-bromosuccinimide (NBS) followed by base-mediated elimination of HBr to afford highly strained exo-bicyclic enamines (**Scheme 57**).



Scheme 57

The ring-opening reactions of **209** were found to proceed well with different nucleophiles (i.e., $TMSN_3$, MeOH, Br^-, OAc, etc.) to afford high yields of **210** with excellent diastereoselectivity. The reactions are regioselective and preferentially give the corresponding pyrrolidine or piperidine precursors by ring opening at the α-position. The resulting enamines are tautomerized into the thermodynamically more stable cyclic imines **210**. Aziridine ring opening can also be triggered by hydrazinolysis with hydrazine. In the case of bicyclic aziridine **211**, this reaction afforded the novel rearranged aziridine **212** (**Scheme 58**) <2003JA14242>.



Scheme 58

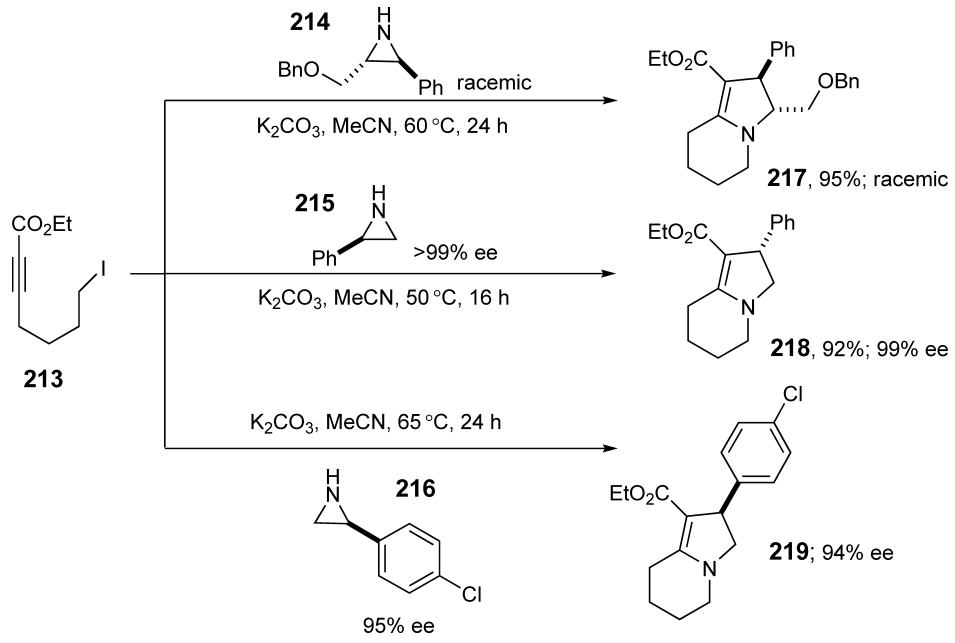
1.01.5.2.4 S_N2/Formal [3+2] cycloaddition route

An interesting formal S_N2/[3+2] cycloaddition route for the synthesis of substituted indolizidines has been reported <2005OL5545>. This reaction requires both an electron-withdrawing group on the alkyne and an aromatic ring on the aziridine. The reaction goes through an initial N-alkylation of the aziridine with iodide **213** followed by a Michael addition/rearrangement to generate indolizidines **217–219** (**Scheme 59**).

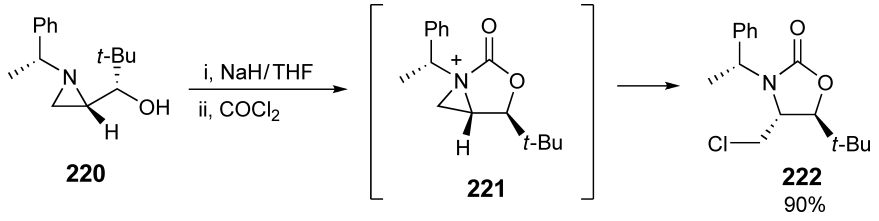
1.01.5.3 Rearrangement Chemistry

1.01.5.3.1 Nonthermal rearrangements

N-Substituted hydroxymethylaziridines undergo an interesting ring expansion in the presence of phosgene, which involves initial nucleophilic behavior of the nitrogen center. Thus, treatment of aziridine **220** leads to the formation of a short-lived bicyclic intermediate **221**, which suffers nucleophilic ring opening by chloride to give the chloromethyloxazolidinone **222** with retention of stereochemistry at both chiral centers. The use of 1 equiv of sodium hydride is necessary to prevent the buildup of hydrochloric acid during the reaction, which tends to cause an unwanted ring opening of unreacted aziridine (**Scheme 60**) <2003JOC43>. A similar rearrangement to oxazolidinones is known to occur upon treatment of aziridines with di-*tert*-butyl dicarbonate ($(t\text{-BOC})_2O$) <2003T677>.

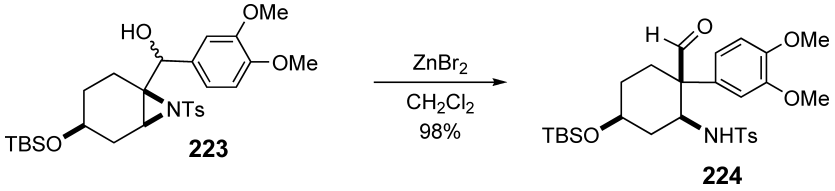


Scheme 59



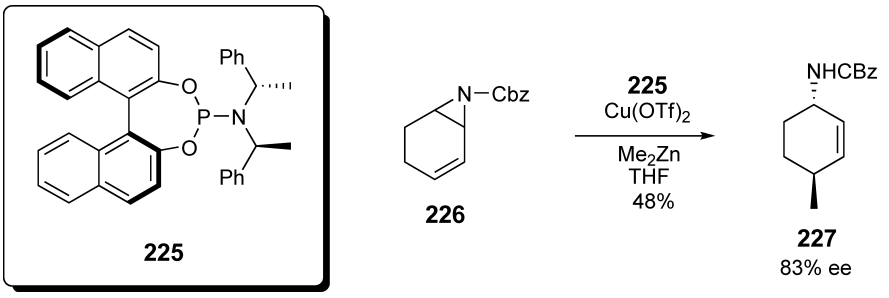
Scheme 60

Hydroxymethylaziridines of this type can also be induced to engage in a Lewis acid-mediated rearrangement to the corresponding aminocarbonyl compound. Thus, the bicyclic tosylaziridine **223** provided **224** in near-quantitative yield when treated with zinc bromide in methylene chloride. The rearrangement involves a stereospecific 1,2-migration of the aryl group. The latter compound was used as a key intermediate in the synthesis of mesembrine (**Scheme 61**) <2003OL2319>.



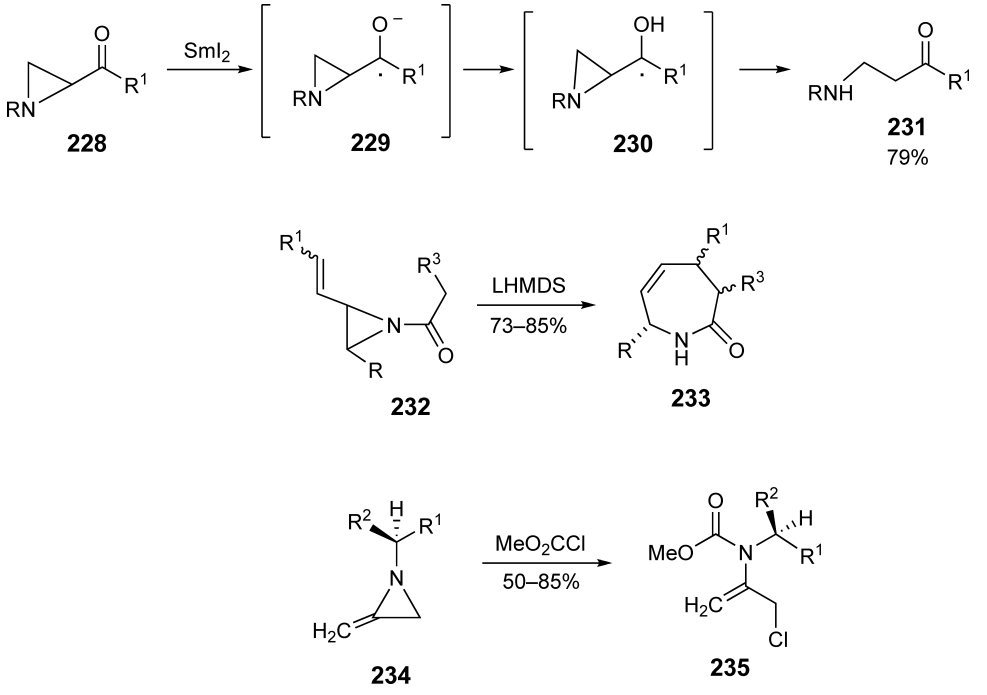
Scheme 61

When aziridines bear a 2-alkenyl substituent, they can engage in an S_N2' reaction with dialkylzinc reagents using copper catalysts. Enantioselectivity can also be induced by including a chiral ligand, such as the binaphthyl phosphoramidite **225**. For example, the aziridinyl cyclohexane **226** provided exclusively the *trans*-1,4-adduct with 83% ee upon treatment with dimethylzinc in the presence of copper(II) triflate and ligand **225** (**Scheme 62**) <2003TL8559>.



Scheme 62

Various functionalized aziridines can undergo some interesting rearrangement chemistry. For example, α-carbonyl aziridines **228** can be smoothly ring-opened upon treatment with samarium iodide. This reaction proceeds via familiar radical anion formation **229** followed by rearrangement to give the β-amino carbonyl **231** <1997T8887>. Vinylaziridines **232** undergo a highly stereoselective aza-[3,3]-Claisen rearrangement to give seven-membered lactams **233** <1995JOC6660, 1997JA8385>. The reaction is rapid and is tolerant of many nitrogen protecting groups. Methyleneaziridines **234** provide enamines **235** when treated with methyl chloroformate in dichloromethane at room temperature (**Scheme 63**) <1997TL5887>.



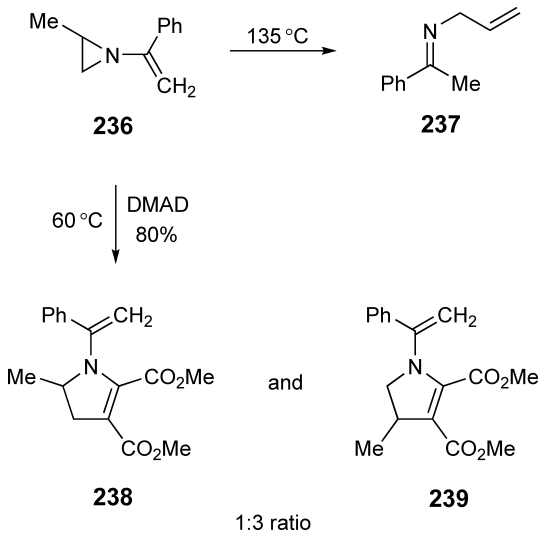
Scheme 63

1.01.5.3.2 Thermal rearrangements

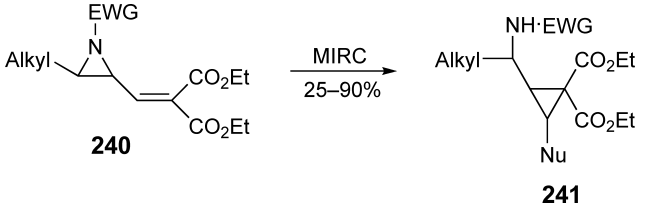
Heating an *N*-alkenyl-substituted aziridine such as **236** at 135 °C afforded **237**, the product derived from a thermal 1,5-hydrogen shift <2005OL1161>. When the thermolysis was carried out in the presence of dimethyl acetylenedicarboxylate, formal [3+2] cycloaddition products were obtained in yields ranging from 65% to 80%. The products were obtained as a mixture of two regioisomers depending on which carbon center of the aziridine ring participated in the cyclization (**Scheme 64**).

Rearrangements of complex aziridines can also result in interesting cyclic structures. For example, Zwanenburg and co-workers <1996T12253> have applied the Michael reaction-induced ring-closure (MIRC) reaction to aziridinyl

methylenemalonates **240**. Interestingly, this produces *cis*-cyclopropane derivatives **241** preferentially, in contrast to the analogous epoxide reactions. The results suggest that steric interactions between the nucleophilic reagent and the substituents of the aziridine ring direct the stereochemistry of the process (**Scheme 65**).



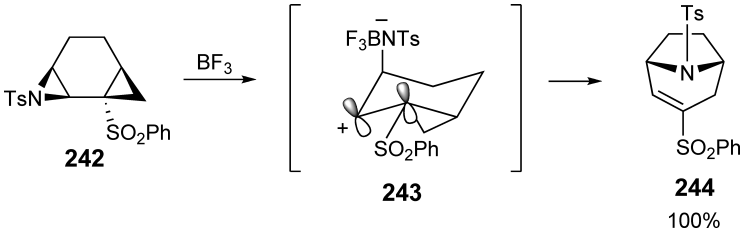
Scheme 64



Scheme 65

1.01.5.3.3 Acid–base rearrangements

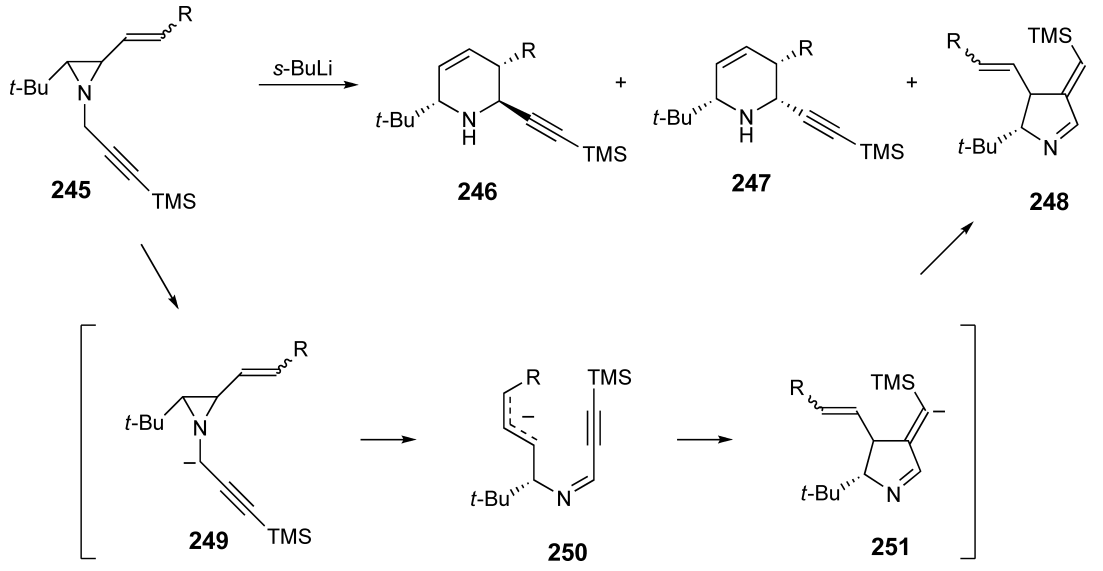
Aziridinocyclopropanes **242** derived from 2-phenylsulfonyl-1,3-dienes undergo BF_3-induced rearrangement to bicyclic amines **244**, which feature the skeleton of the tropane alkaloids. The reaction proceeds via cyclopropyl carbinyl cation **243**, an intermediate also invoked in the analogous epoxide rearrangements. Trapping by fluoride ion is a competing pathway (**Scheme 66**) <1996TL3371>.



Scheme 66

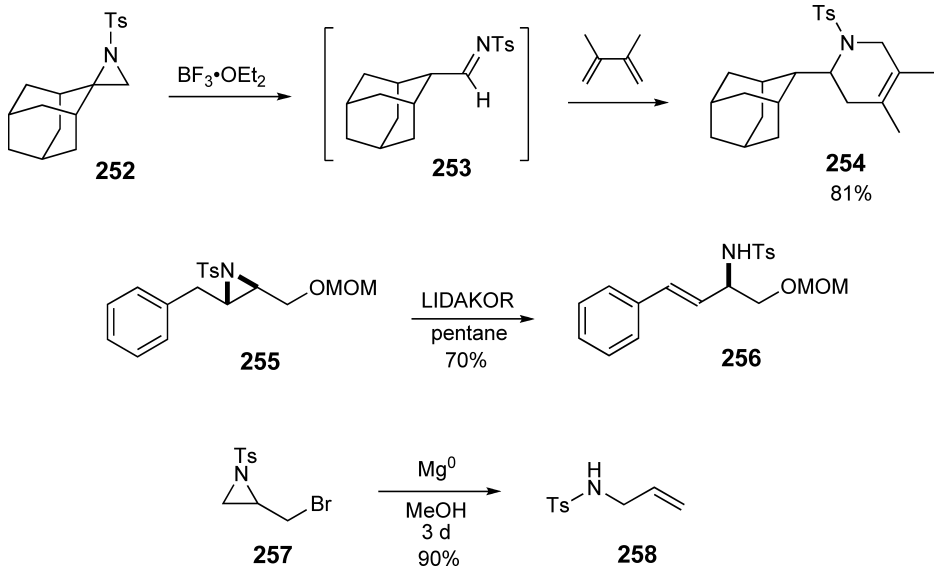
A novel rearrangement of *N*-propargyl vinylaziridines **245** under Wittig rearrangement conditions has been reported. Thus, treatment of **245** with *s*-BuLi led to the formation of the expected tetrahydropyridines **246** and **247**, products of an aza-[2,3]-Wittig rearrangement, along with significant amounts of pyrroline **248**. The formation of this latter product was surprising, and studies were carried out to elucidate the reaction pathway. Deuterium labeling

experiments indicate that the mechanism involves opening of the aziridine ring by an initially formed propargylic anion (cf. **249**) to give the corresponding allylic anion (cf. **250**), which then undergoes a 5-*exo*-*dig*-cyclization to form a vinylic anion (cf. **251**) (**Scheme 67**) <1996TL2495>.



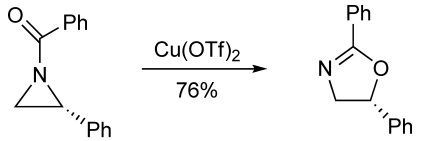
Scheme 67

The same ring strain that lends aziridines reactivity toward nucleophiles also makes them prone to ring-opening isomerizations and rearrangements. For example, the tetracyclic aziridine **252** underwent aza-pinacol rearrangement in the presence of boron trifluoride to give the tosyl imine **253**, which in turn could be trapped as the Diels–Alder adduct **254** <2002CC134>. Alternatively, base-catalyzed eliminative ring opening can be promoted with superbasic mixtures such as lithium diisopropylamide/potassium *t*-butoxide (LIDAKOR), as illustrated by the conversion of the protected aziridinyl alcohol **255** to the allyl amine derivative **256** <2002T7153, 2002CC778>. In the case of α-bromo aziridines (e.g., **257**), this elimination to allylamines can be promoted by electron transfer from magnesium metal in methanol (**Scheme 68**) <2002T7145>.



Scheme 68

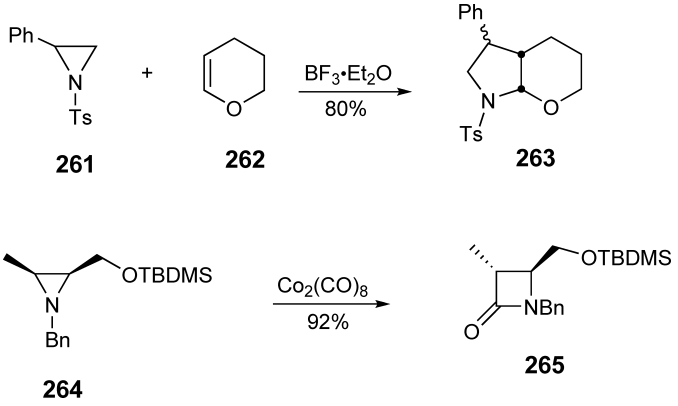
Acylaziridines have been stereospecifically rearranged to give oxazolines, as illustrated by the copper(II) triflate-catalyzed conversion of the chiral aziridine **259** into (*R*)-oxytriphine **260**. Mechanistically, this transformation is believed to proceed via initial coordination of the amide nitrogen with the 'azaphilic' Lewis acid. This leads to the formation of an intermediate carbocation that exists as a tight ion pair in order to preserve the stereochemistry of the rearrangement (**Scheme 69**) <1998JOC4568>.



259 **260**

Scheme 69

Certain aziridines have been shown to engage in some interesting ring-expansion reactions. For example, phenylaziridine **261** behaved as a 1,3-dipole toward dihydropyran **262** in the presence of boron trifluoride etherate to give the bicyclic species **263**, which can be subsequently converted to substituted pyrrolidines <1999TL5315>. The silylated hydroxymethyl aziridine **264** undergoes carbonylative ring expansion promoted by dicobalt octacarbonyl to provide the functionalized β-lactam **265**, a process which proceeds with inversion of configuration (**Scheme 70**) <1999JOC518>.



261 **262** **263**

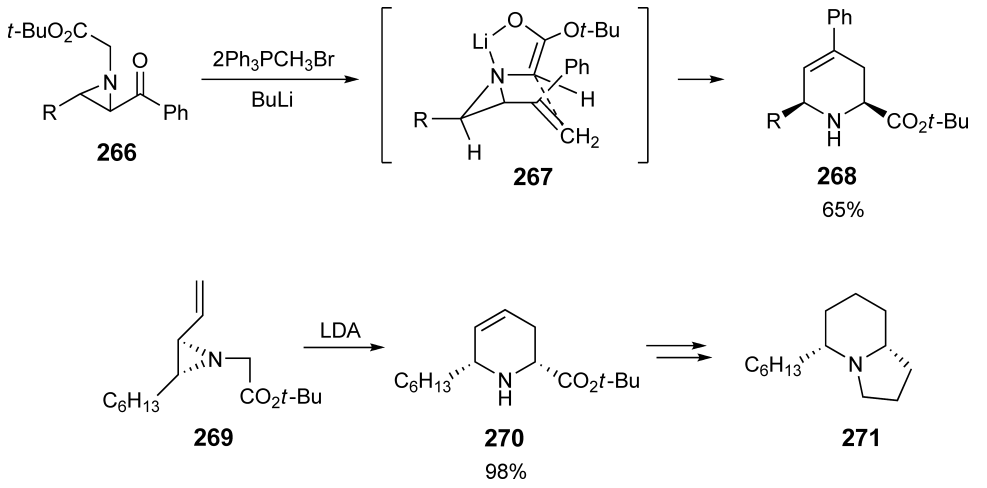
264 **265**

Scheme 70

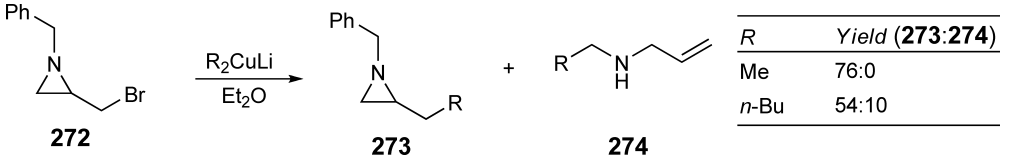
Coldham *et al.* <1995TL3557> and Somfai <1994CC2785> have independently investigated the ring expansion of vinyl aziridines to piperidines. Thus, Coldham *et al.* have prepared the unsaturated *cis*-piperidines **268** as single diastereoisomers in fair to good yield from the keto-aziridines **266** using a one-pot, two-step procedure. The stereochemical outcome is rationalized on the basis of the chelated intermediate **267**. In a related manner, Somfai has used this protocol for the enantioselective total synthesis of indolizidine 209D **271**, starting from aziridine **269** (**Scheme 71**).

De Kimpe and co-workers have found that (2-bromomethyl)-*N*-alkyl aziridines react with organocuprate reagents to provide largely the product of bromide displacement, **273** <2005SL931>. Most aliphatic organocuprates (e.g., R = Me, *n*-Bu) provide good yields of the displacement product **273**. When R = allyl, the sole product is **274** (40%), presumably via a competing electron-transfer or metal–halogen exchange reaction which then leads to ring opening (**Scheme 72**).

Aziridines can undergo a variety of synthetically useful rearrangement reactions which provide new heterocyclic species, as exemplified by the microwave-assisted ring expansion of *N*-acetyl 3′-aziridines **275** to oxazolines **276** <2001T2807, 2001EJO3545>, the formation of pyrrolines **279** in the presence of acrylonitrile and solid sodium hydroxide <2001T6993>, and thermal ring opening to a 1,3-dipole followed by capture with electron-rich alkenes to provide substituted pyrrolidines **282** (**Scheme 73**) <2001TL6087>.

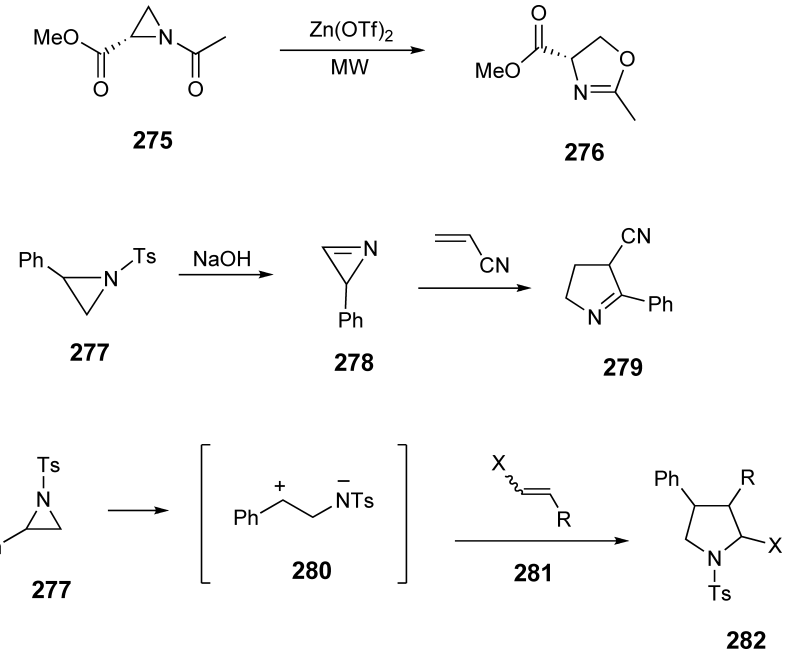


Scheme 71



R	*Yield* (**273**:**274**)
Me	76:0
n-Bu	54:10

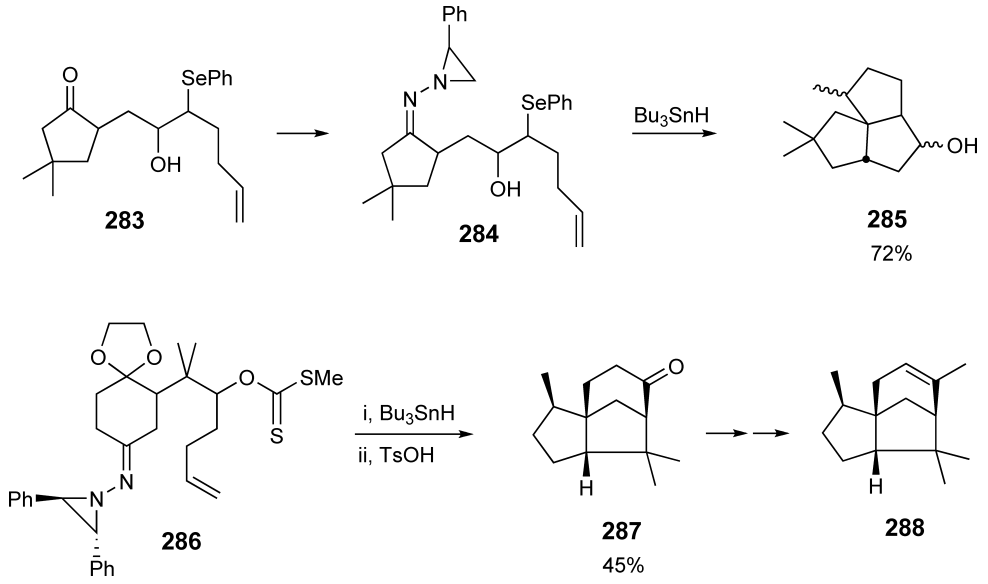
Scheme 72



Scheme 73

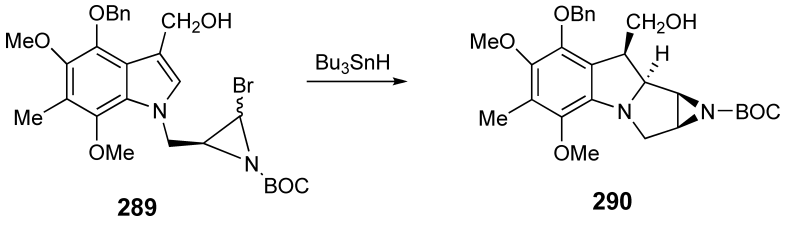
1.01.5.4 Radical Reactions

The aziridine functionality can also be synthetically useful in radical-based reactions. For example, the aziridinylimine group in the phenylselenane **284** serves as a convenient precursor for the generation of a radical center. The resulting carbon-based radical undergoes sequential cyclization to provide the tricyclic alcohol **285** in 72% yield <1998SL981>. A similar sequence, using a chiral aziridine, was employed as a key reaction in a novel synthesis of α-cedrene **288** (**Scheme 74**) <1998TL7713>.



Scheme 74

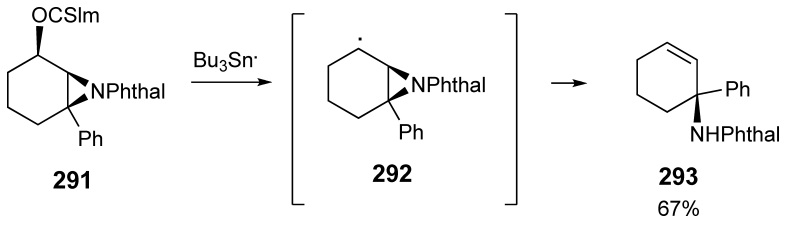
Radical centers can also be generated on the aziridine ring itself, which can then take part in further reaction with preservation of the heterocyclic entity. This process is demonstrated by the radical cyclization of the highly functionalized indole **289** to give the tetracyclic aziridine **290** in fair overall yield (**Scheme 75**) <1998TL2455>.



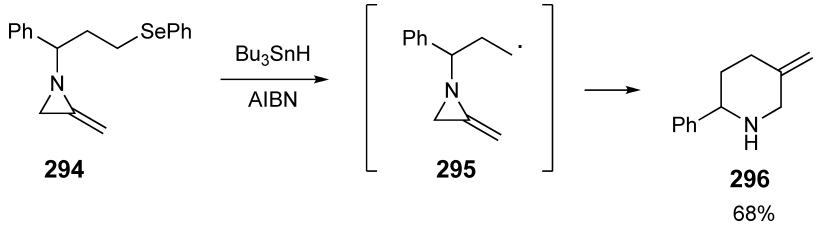
Scheme 75

Aziridinylcarbinyl radicals (e.g., **292**) are interesting reactive intermediates and were shown to undergo β-cleavage to form aminoalkenes (e.g., **293**), which are the products of C–N bond cleavage. The selectivity of the ring opening was rationalized on the basis of more effective overlap of the singly occupied π-orbital on the radical center with the C–N bond (**Scheme 76**) <1999TL4873>.

An interesting radical variant involves the intramolecular 5-*endo*-cyclization of 3-(2-methyleneaziridin-1-yl)propyl radicals **295** to methylenepiperidine derivatives **296** (**Scheme 77**) <2001OL2383>.



Scheme 76



Scheme 77

1.01.5.5 [3+2] Cycloaddition Chemistry

1.01.5.5.1 Azomethine ylide generation

Another interesting and synthetically useful reaction of aziridines is their tendency to open thermally to azomethine ylides, a process which can also be facilitated by Lewis acid catalysts. These reactive intermediates can be trapped by a variety of dipolarophiles to give new heterocyclic species. Methyl vinyl ethers convert aziridines such as **298** into a pyrrolidine derivative (i.e., **300**) in the presence of a zinc(salen) Lewis acid catalyst **297** (Salen = *N*,*N*′-bis(salicylaldehydo)ethylenediamine) <2004JA2294>. Similarly, nitriles (e.g., **302**) lead to the formation of 2,4-disubstituted-1*H*-imidazolines (e.g., **303**) under the catalysis of boron triethyloxonium tetrafluoroborate <2004TL1137>. Under almost-identical conditions, the aziridine–Lewis acid complex can be trapped with π-nucleophiles, such as a tethered olefin, to provide fused bicyclic pyrrolidines (e.g., **305**) <2004TL5011>. The reader is directed to a recent review dealing with the intramolecular dipolar cycloaddition reactions of azomethine ylides derived from substituted aziridines (**Scheme 78**) <2005CRV2765>.

1.01.5.6 [3+3] Annelation of Aziridines

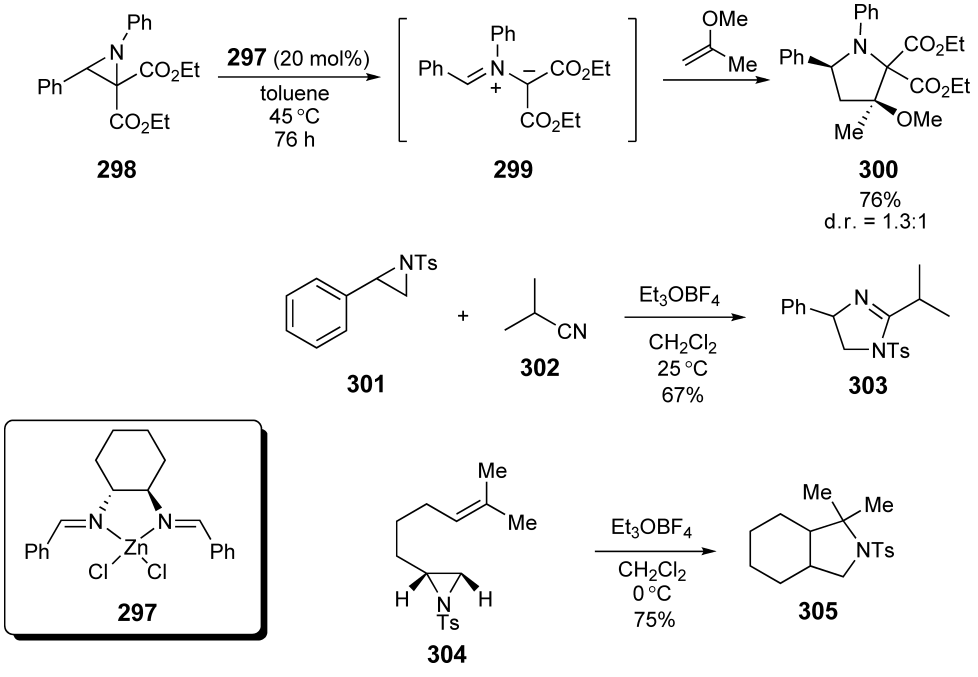
1.01.5.6.1 Stereoselective synthesis of functionalized piperidines

Work in the Harrity labs has focused on exploiting aziridines for the stereoselective synthesis of functionalized piperidines through a [3+3] annelation strategy. The initial studies centered on the employment of Trost's conjuctive reagent **306** in tandem with a palladium catalyst to deliver a series of enantiopure 2-alkyl piperidines with an exomethylene moiety at C-5 <2001SL1596, 2003JOC4286, 2003OL3427>. *N*-Tosyl-protected 2-substituted aziridines **307** underwent regioselective addition of the Pd–TMM complex at the least-hindered site and furnished the functionalized piperidines **308** (TMM = trimethylenemethane). This technique provides an expedient route to enantiopure 2-piperidines because the precursor aziridines are readily prepared in enantiomerically pure from the corresponding amino acids (**Scheme 79**) <1992SL41>.

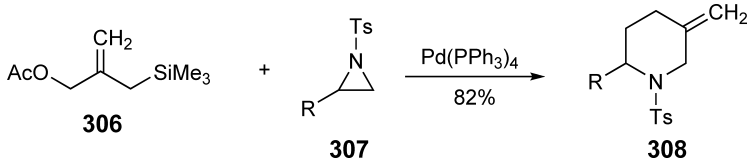
1.01.5.6.2 Grignard addition–cyclization reaction for piperidine synthesis

More recently, a stepwise formal [3+3] cycloaddition sequence via a Grignard addition–cyclization reaction leads to a much improved piperidine synthesis <2005OL2993>. This methodology provides improved flexibility in both the aziridine substrate and TMM equivalent. Double deprotonation of methallyl alcohol, transmetallation with $MgBr_2$, and addition to aziridine **309** gave the corresponding adduct **310** in excellent yield. The Mitsunobu reaction of **310** provided the trisubstituted piperidine **311** in high yield but as an equal mixture of diastereomers at C-6 (**Scheme 80**). In a similar vein, a stepwise [3+3] annelation sequence was carried out by addition of the Büchi Grignard reagent **312** to aziridines. The initially formed ring-opened intermediate **313** was subjected to an acid-catalyzed deprotection–cyclization protocol

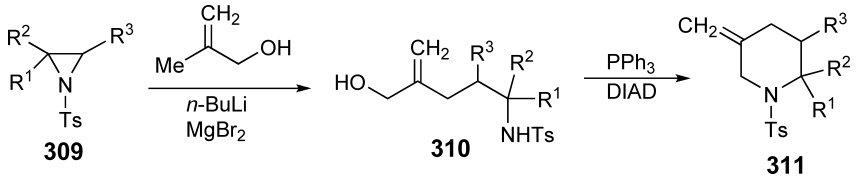
to produce tetrahydropyridine **314**, without loss of enantiopurity over the two steps. The methodology was used in the stereoselective synthesis of the alkaloid (−)-dihydropiridine. A similar [3+3] strategy was used by the Harrity group for the synthesis of several *Nuphar* alkaloids <2005JOC207> as well as for a formal synthesis of (±)-perhydrohistrionicotoxin (**Scheme 81**) <2006TL331>.



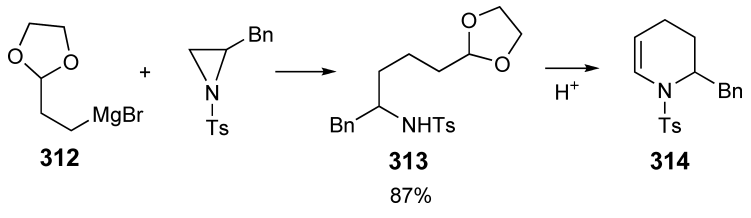
Scheme 78



Scheme 79



Scheme 80

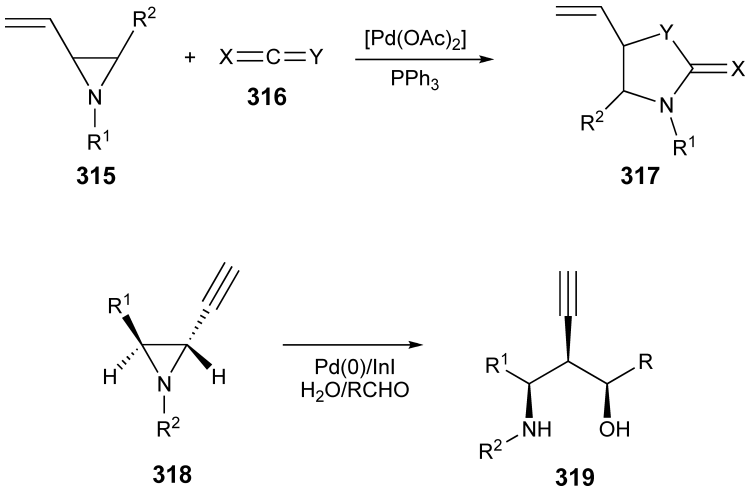


Scheme 81

1.01.5.7 Ring-Expansion Reactions

1.01.5.7.1 Ring expansion with heterocumulenes

Vinyl and alkynyl aziridines exhibit particularly interesting chemistry in the presence of palladium catalysts. Thus, 2-vinylaziridines undergo cycloaddition reactions with various heterocumulenes in the presence of $Pd(OAc)_2$ and triphenylphosphine to give new five-membered heterocycles **317** in moderate to high yields. The mechanism is believed to involve an η^3–η^1–η^3-interconversion of a (π-allyl)palladium intermediate <2000JOC5887>. Conversely, treatment of 3-alkyl-2-ethynyl-aziridines **318** with indium iodide in the presence of $Pd(PPh_3)_4$ and water gives intermediate allenylindium reagents which can undergo *in situ* addition onto aldehydes to afford 2-ethynyl-1,3-amino alcohols **319** bearing three chiral centers (**Scheme 82**) <2000OL2161>.



Scheme 82

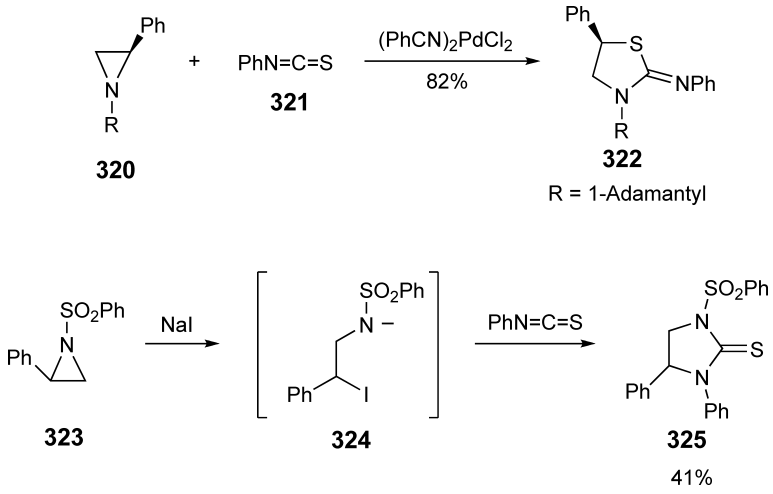
Alper and co-workers have reported the first enantiospecific palladium-catalyzed cycloaddition of aziridines with heterocumulenes. Thus, *N*-butyl phenylaziridine **320** reacts with *p*-chlorophenyl isothiocyanate in the presence of $(PhCN)_2PdCl_2$ to form thiazolidinimine **322** in good yield. This reaction proceeds with retention of configuration at the aziridine carbon center <1995JA4700>. Nadir and Basu have reported a very similar reaction involving the aziridine sulfonamide **323** and using sodium iodide as a catalyst. Based on spectroscopic evidence, these conditions provide the isomeric 2-imidazolidine-thione **325** rather than the thiazolidinimine. The reaction is believed to proceed via initial attack of iodide at the benzylic position to give an intermediate iodoamide **324**, which then condenses with the heterocumulene (**Scheme 83**) <1995JOC1458>.

1.01.5.7.2 Ring expansion with isocyanates

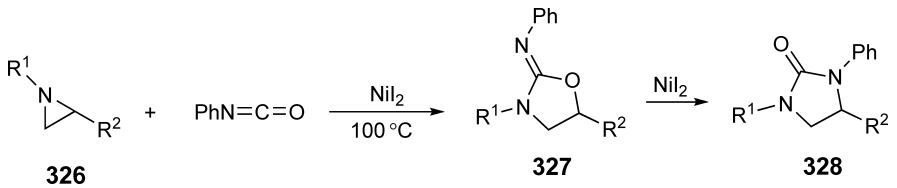
Cycloaddition of aziridines **326** with isocyanates proceeds smoothly in the presence of nickel catalysts and five-membered heterocycles **327** were isolated in good to high yields <2006OL379>. The best result was obtained when the reaction was carried out in the presence of NiI_2. A longer reaction time resulted in the isomerization to the corresponding imidazolidinone derivative **328**. The mechanism suggested for the reaction involves cleavage of the aziridine ring by nucleophilic attack of iodide derived from NiI_2. The resulting ring-opened nickel amine is a strong nucleophile and subsequently attacks the isocyanate to give the iminooxazolidine **327**. The subsequent isomerization proceeds to give the thermodynamically more stable isomer **328** (**Scheme 84**).

Enantiomerically pure N,N-disubstituted imidazolidine-2-one-4-carboxylates **332** can also be obtained in a one-step, simple, and highly efficient manner using a Lewis acid-catalyzed ring-expansion reaction of commercially available chiral aziridines with isocyanates. These reactions proceed both regio- and stereospecifically with retention of the configuration at the C-2 carbon of the chiral aziridines <2005CC3062>. The C(2)–N bond of the aziridine

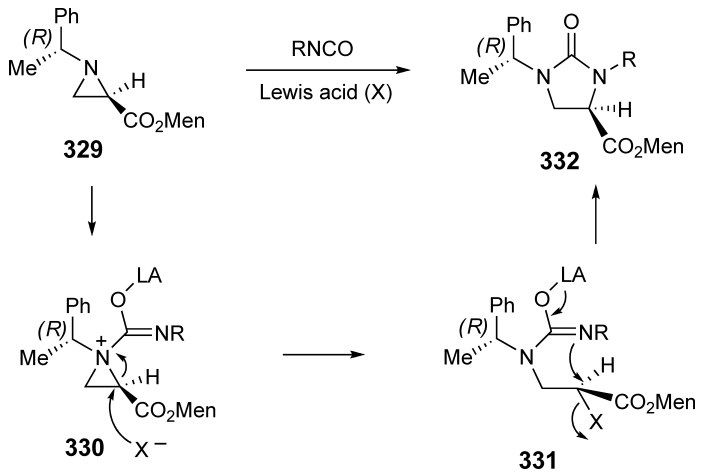
is regiospecifically cleaved by the bromide ion from $MgBr_2$ or the chloride ion from TMSCl via an S_N2 process as in **330**, and then an intramolecular cyclization by the urea amide nitrogen of **331** gives the corresponding imidazolidinone **332** which corresponds to overall retention of the configuration at C-2 of the orginal aziridine **329** (**Scheme 85**).



Scheme 83



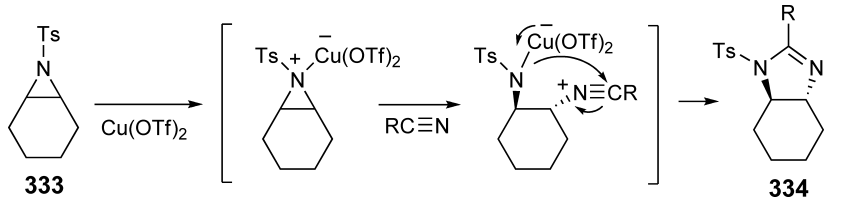
Scheme 84



Scheme 85

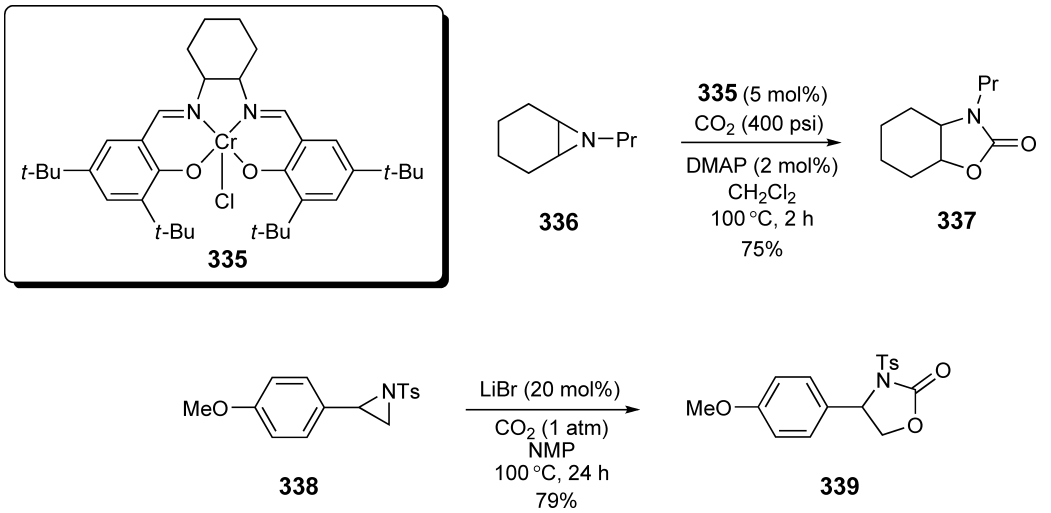
1.01.5.7.3 Ring expansion with nitriles

A direct and efficient route to imidazoline and pyrrolidine derivatives using copper(II) triflate-mediated [3+2] cycloaddition of various aryl, alkyl, and cycloalkyl *N*-tosylaziridines with nitriles and olefins as dipolarophiles has been reported <2006TL5399>. Formation of bicyclic imidazoline **334** with a *trans*-ring junction as a single product from aziridine **333** suggested that the reaction proceeded through an S_N2-type pathway (**Scheme 86**).



Scheme 86

The (salen)chromium complex **335** was shown to promote the insertion of carbon dioxide into aziridines (e.g., **336**) to yield the corresponding oxazolidinones (e.g., **337**), whereby the substrate is treated with CO_2 under high pressure (Parr reactor) in the presence of catalytic quantities of **335** and dimethylaminopyridine (DMAP) <2004OL2301>. Considerably milder conditions have been reported independently, in which lithium bromide serves as catalyst in a medium of *N*-methylpyrrolidone (NMP). For example, aryl aziridine **338** was converted to oxazolidinone **339** in 79% yield over 24 h. Use of the more-polar and higher-boiling solvent allows for delivery of CO_2 using a balloon at atmospheric pressure. Electron-donating substituents tend to accelerate the reaction (**Scheme 87**) <2004TL1363>.

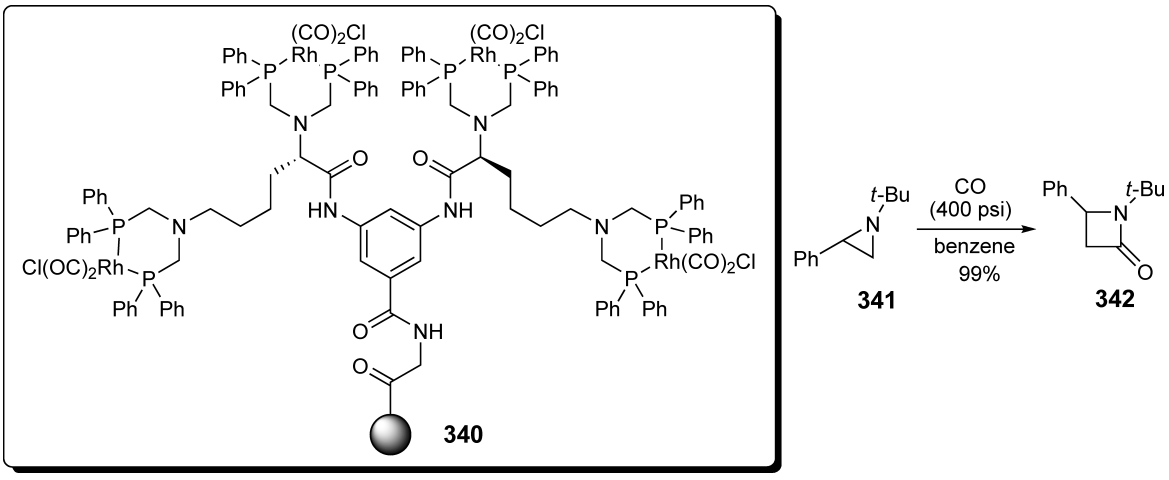


Scheme 87

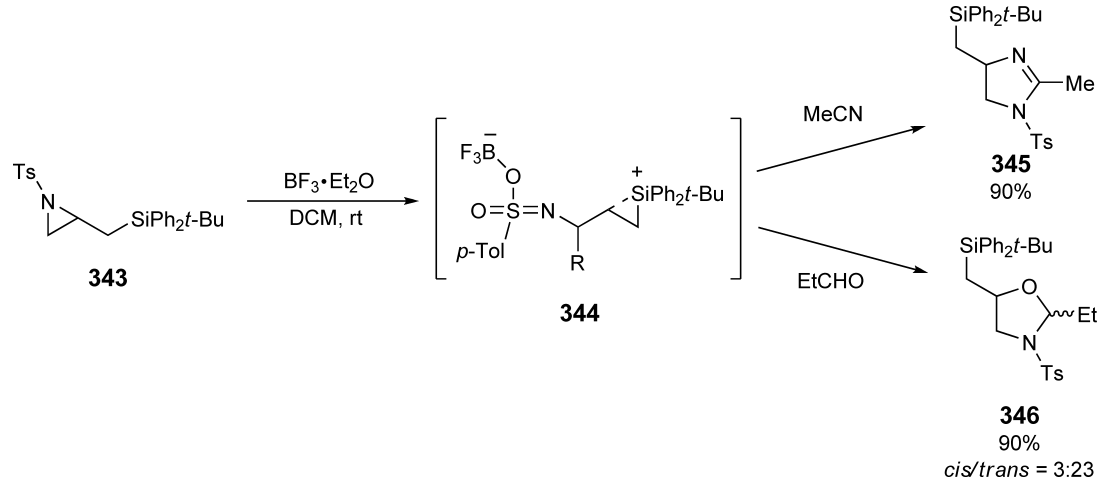
1.01.5.7.4 Carbonylative ring expansion

In a similar vein, a resin-supported rhodium-complexed dendrimer **340** has been shown to promote the carbonylative ring expansion of aziridines to β-lactams, as illustrated by the conversion of the *N*-*t*-butyl aziridine **341** to the corresponding lactam **342** in almost quantitative yield. The supported catalyst, which shows reactivity comparable to the solution-phase variety, is easily recovered by filtration and exhibits no significant loss of activity upon recycling (**Scheme 88**).

The silicon β-effect has been exploited to convert aziridines to 2-imidazolines and oxazolidines <2005JA16366>. This reaction presumably goes through siliranium ion **344**, which can then react with an electrophile to form **345** or **346**. It has also been shown that zinc dihalides are effective in catalyzing the formation of **345**, but require elevated temperatures (**Scheme 89**) <2005TL4103>.



Scheme 88



Scheme 89

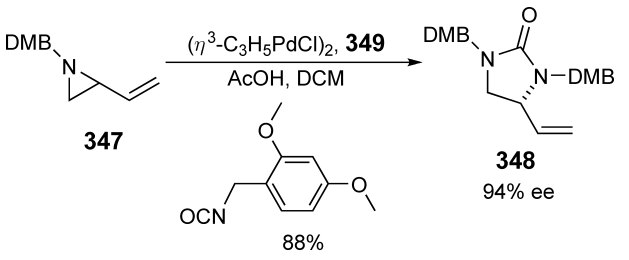
A dynamic kinetic asymmetric transformation (DYKAT) of racemic vinyl aziridine **347** yielded the enantiopure imidazolidinone **348** (**Scheme 90**) <2005OL823>. This transformation was the initial step in a total synthesis of (+)-pseudodistomin D.

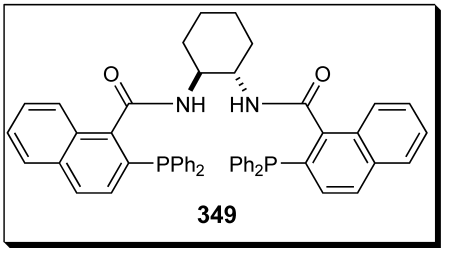
1.01.5.8 Aziridinyl Carbanion Chemistry

1.01.5.8.1 Aziridinyl carbanion with electron-withdrawing substituent

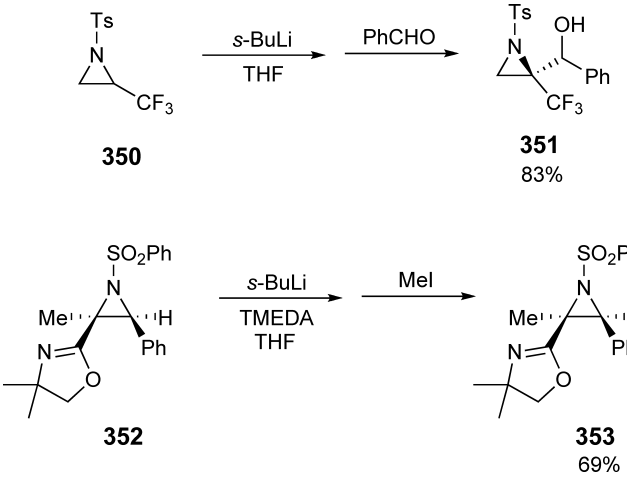
When one of the carbon atoms in the aziridine ring is equipped with an electron-withdrawing substituent, these substrates can often be cleanly deprotonated and used for subsequent carbanion chemistry. For example, the anion derived from the trifluoromethyl aziridine **350** engages in nucleophilic addition onto benzaldehyde to give the aziridinyl alcohol **351** in 83% yield <2003TL6319>. Similarly, deprotonation of the oxazolinylaziridine **352** followed by treatment with methyl iodide gave mainly the methylated product **353** (**Scheme 91**) <2003TL2677>.

Sulfinylaziridines **354** can be converted to the corresponding carbanion **355** upon treatment with *t*-butyllithium. This anion has been captured with various electrophiles to give substituted aziridines **356** (**Scheme 92**) <1998TL2345>.

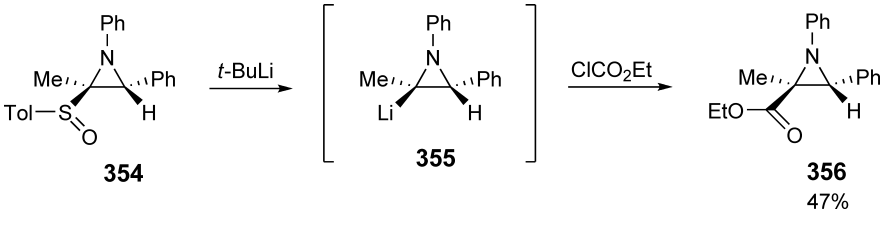




Scheme 90

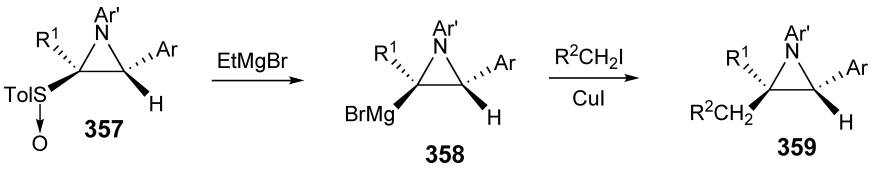


Scheme 91



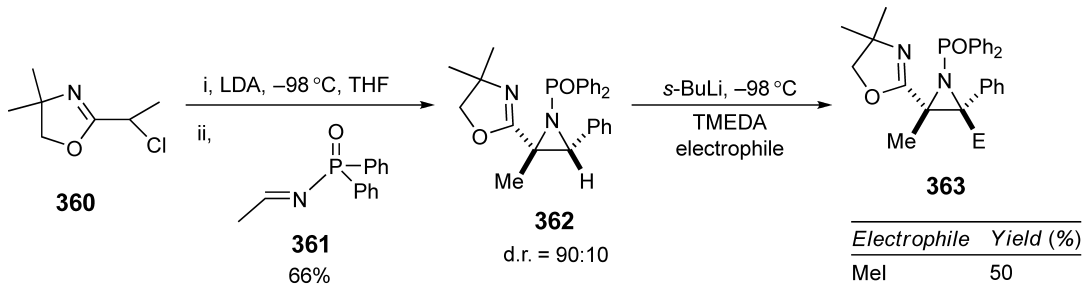
Scheme 92

Sulfinylaziridines of type **357** were found to undergo a clean metallation by ethyl Grignard with loss of the sulfoxide moiety to give the aziridinyl anions **358**, which in turn can be alkylated in the presence of copper(I) iodide to give new elaborated products **359** with the heterocyclic nucleus intact (**Scheme 93**) <2000TL6495>.



Scheme 93

The Darzens reaction of the oxazoline **360** with a series of aldimines has been shown to form aziridine **362** in good yields and with high diastereoselectivity <2005T3251>. Deprotonation of the aziridine to form the aziridinyl anion and subsequent reaction with an electrophile provide the highly substituted aziridines **363** in moderate yields. The diphenylphosphinyl group on the nitrogen provides optimal yields in the lithiation reaction (**Scheme 94**).



Electrophile	*Yield (%)*
MeI	50
BnBr	58
PHCHO	24

Scheme 94

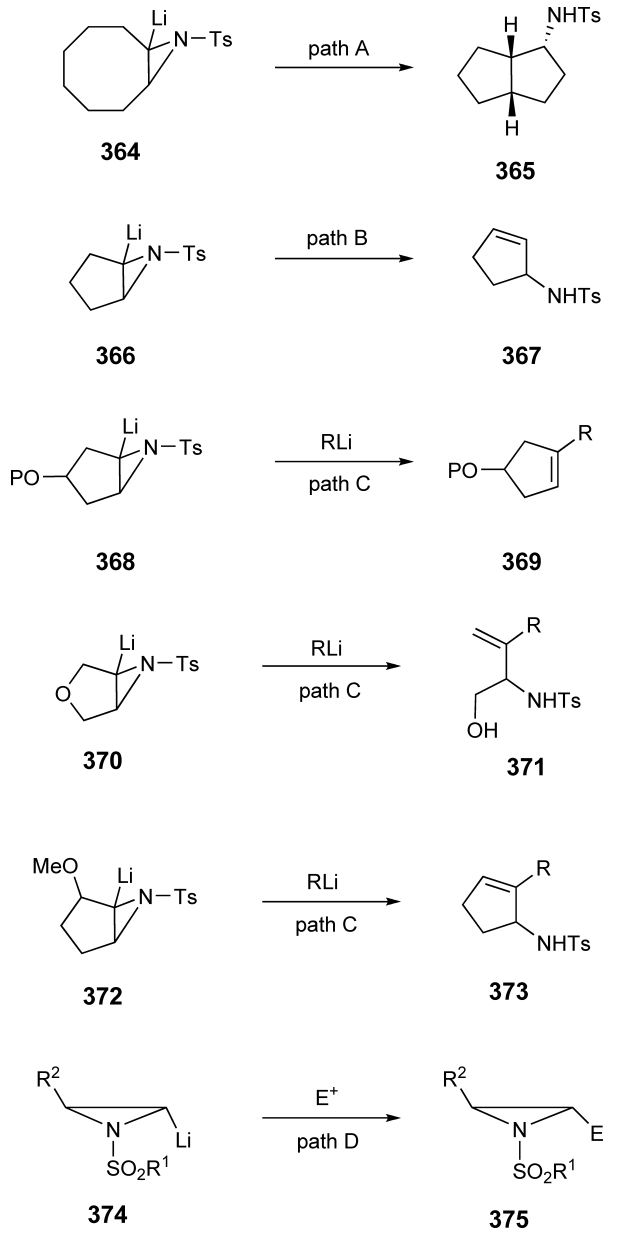
1.01.5.8.2 Reactions of lithiated *N*-sulfonylaziridines

In recent years, there has been significant interest in the development of novel synthetic transformations of lithiated *N*-sulfonylaziridines <2005CC5696, 2006OL995, 2001HCA662, 2004HCA227, 2003TL6613>. For lithiated aziridines generated by aziridine deprotonation using strong bases, at least four different reaction modes are known. Path A corresponds to an insertion into a CH bond. A typical example involves the transannular CH insertion reaction of **364** to give **365**. Path B involves insertion into an adjacent β-CH bond to produce an allylic amine (i.e., **366** → **367**). Path C proceeds by insertion into an organolithium reagent. This process has been referred to as a 'reductive alkylation' reaction and can occur with loss of the amino group to give alkenes <2003T9779>. The amino group can also be retained with the generation of a substituted allylic amine if there is a β-alkoxy group present (i.e, **370** → **371** and **372** → **373**) <2004CC2234, 2004OL4817>. Finally, path D involves the electrophilic trapping of lithiated terminal aziridines (i.e., **374** → **375**) (**Scheme 95**).

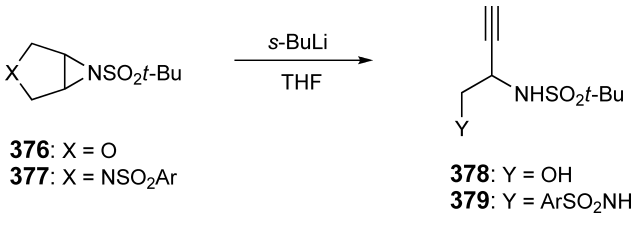
Recently, the O'Brien group has disclosed a new organolithium-mediated transformation of aziridines that had not been previously encountered <2005CC5696>. Thus, dihydrofuran **376** and dihydropyrrole *N*-benzenesulfonyl aziridine **377** were converted into alkynyl amino alcohols **378** and diamines **379**, respectively, using *sec*-butyllithium–PMDETA in THF (PMDETA = pentamethyldiethylenetriamine). The methodology provides an alternate and more direct route to protected alkynyl amino alcohols which are normally prepared in four to six steps from serine and have proved to be useful in the synthesis of natural and unnatural amino acids containing alkynyl, alkenyl, and cyclopropyl functionality (**Scheme 96**) <2003EJO3219>.

1.01.5.8.3 Trapping of lithiated *N*-sulfonylaziridines with electrophiles

Regio and stereoselective deprotonation of *N*-Bus (Bus = *t*-butylsulfonyl)-protected terminal aziridines **380** with lithium 2,2,6,6-tetramethylpiperidide proceeds smoothly to generate a nonstabilized aziridinyl anion **381** that undergoes *in situ* or external electrophile trapping to give *trans*-disubstituted aziridine **382** in good to excellent yields. No significant degradation of ee was observed during the deprotonation–*in situ* silylation of an enantio-enriched terminal aziridine <2005OL1153>. Anion trapping could be carried out with enolizable and nonenolizable carbonyl compounds, DMF, benzenesulfonyl fluoride, and carbon dioxide. While there are other indirect methods for aziridinyl

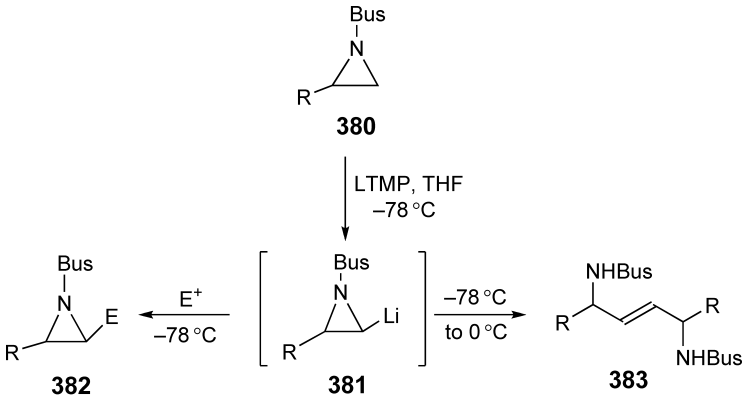


Scheme 95



Scheme 96

anion generation and electrophile trapping <1996CR3303, 1993JA1607, 2003T9803, 2003T9849>, this procedure is attractive because it proceeds directly from simple terminal aziridines to give *trans*-disubstituted aziridines of type **382**. The latter retain a useful nitrogen protecting group to enable further synthetic transformations. Interestingly, when the temperature used for the deprotonation reaction was allowed to warm to 0 °C, the dimeric 2-ene-1,4-diamine **383** was isolated as the major product. The formation of this product clearly established the carbenoid reactivity of the α-lithiated aziridinyl anion **381** (**Scheme 97**) <2006AGE935>.

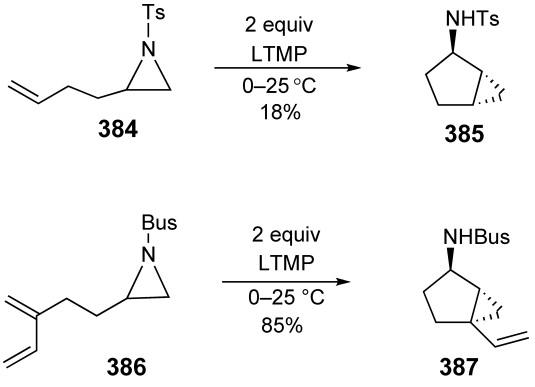


Electrophile	*R*	*Yield (%)*
TMSCl	$SiMe_3$	86
PhCHO	CHOHPh	38
DMF	CHO	63
CO_2	CO_2Me	63

Scheme 97

1.01.5.8.4 Intramolecular cyclopropanation of lithiated *N*-sulfonylaziridines

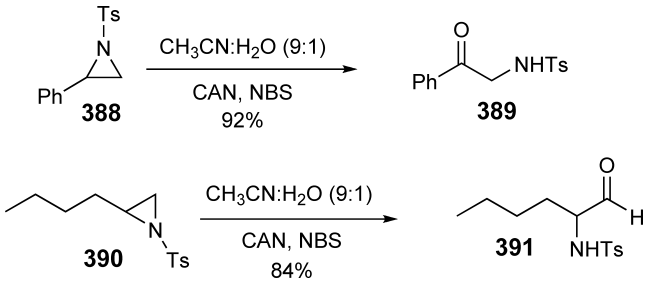
More recently, Hodgson *et al.* have found that aziridinyl anions can also undergo a diastereoselective intramolecular cyclopropanation reaction to give 2-aminobicyclo[3.1.0]hexenes in good yield <2006OL995>. Reversing the addition order so that the aziridine was added dropwise to the base led to increased yields of the bicyclic amine. When the dienyl-substituted aziridine **386** was used, an 85% yield of the 2-amino bicyclo[3.1.0]hexane **387** was obtained, which contains the potentially useful vinyl cyclopropane moiety (**Scheme 98**).



Scheme 98

1.01.5.9 Miscellaneous Reactions

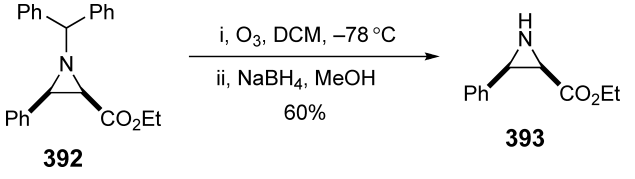
The regioselective oxidation of aziridines to α-tosylamino ketones has been accomplished via NBS and cerium(IV) ammonium nitrate (CAN) <2005TL4111>. Both styryl aziridines, **388**, and aliphatic aziridines, **390**, have been oxidized. A related report uses β-CDs in addition to NBS to catalyze the same transformation <2005TL1299>. These reaction conditions also work well for epoxides to provide the corresponding α-hydroxy ketones (**Scheme 99**).



Scheme 99

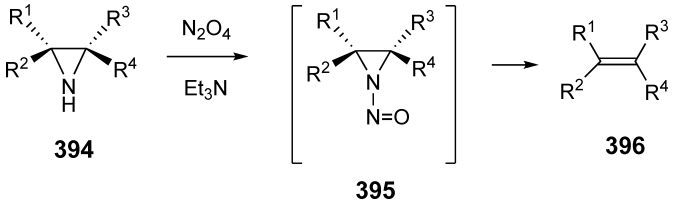
The transformation of aziridines that do not involve ring opening are rare due to the reactivity of the aziridine ring. Considering the somewhat more difficult synthesis of aziridines (relative to epoxides), the ability to convert one aziridine into another represents a significant expansion of the scope of any aziridine synthesis.

The deprotection of N-protected aziridines continues to be a problematic process. Many methods used to deprotect N-protected aziridines result in cleavage of the aziridine ring. The use of ozone to deprotect *N*-benzhydryl aziridines, **392**, has been reported <2005OL2201>. While the yields of this method were modest, this is an important new method for such deprotections (**Scheme 100**).



Scheme 100

An interesting deamination reaction of aziridines was reported, in which treatment of N-unsubstituted aziridines **394** with dinitrogen tetroxide (2 equiv) in the presence of Et_3N results in clean deamination to provide the corresponding alkenes **396** with remarkably high yields (>90%). The reaction is believed to proceed via the *N*-nitroso intermediate **395**, so that the driving force for the reaction is liberation of N_2O (**Scheme 101**) <1999SC1241>.



Scheme 101

1.01.6 Synthesis of Monocyclic Aziridines

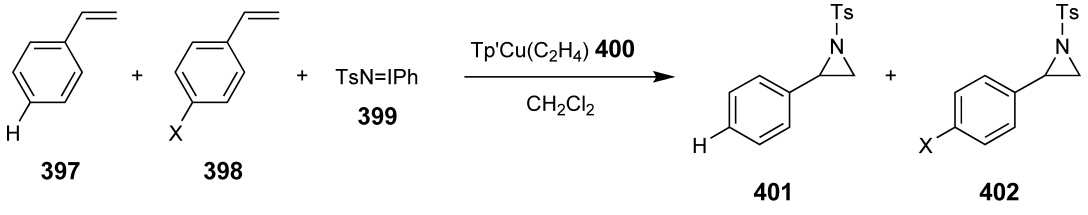
The synthesis of aziridines has been covered earlier in several major review chapters prior to 1995 <2003CRV29057, 2004T2701, B-2006MI1>. Murphree and Padwa have reviewed the literature of aziridine synthesis on a yearly basis, covering the period 1995–2005 <1995PHC43, 1996PHC43, 2000PHC52, 2001PHC52, 2002PHC75, 2003PHC54,

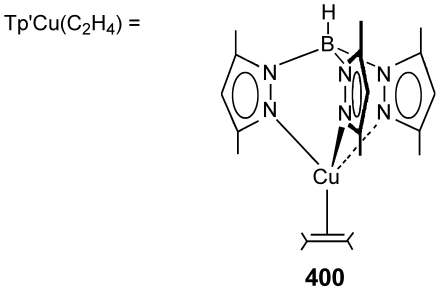
2004PHC55, 2005PHC81>. The synthetic scope of aziridine chemistry has blossomed in recent years, which is evident in a literature search by the term 'aziridine review' resulting in more than 140 hits of review articles in the last four decades. Among them, 40 reviews were published since the year 2000, averaging over six reviews per year. The many reviews on aziridine chemistry all contain sections on their synthesis. Representative examples of all the useful methods for monocyclic aziridine synthesis are presented below. Synthetic methodologies for the preparation of aziridines include nitrenation of alkenes [N+C═C], methylidenation of imines [C+C═N], and cyclization of 1,2-amino alcohols, 1,2-amino halides, and 1,2-azido alcohols. In addition to coverage of new methods published since CHEC-II(1996), later examples of older methods are reported.

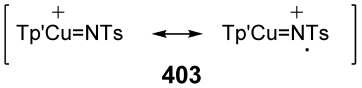
1.01.6.1 Metal-Catalyzed Reactions Using Aryliodanes

Olefin-aziridination reactions are typically accomplished by using a nitrene-transfer reagent. The nitrogen source for this reaction, a nitrene or nitrenoid, can be generated in various ways: (1) thermolytic or photolytic decomposition of organyl azides; (2) base-induced α-elimination of metal halides from metal *N*-arenesulfonyl-*N*-haloamides; (3) α-elimination of HX from an amine or amide with an electronegative atom X (X = halogen, O) attached to the NH group; (4) metal-catalyzed reaction of [*N*-(alkane/arenesulfonyl)imino]aryliodanes; (5) oxidation of a primary amine; and (6) thermally induced cycloreversion. Over the past decade, the metal-catalyzed conversion of [*N*-(alkane/arenesulfonyl)imino]aryliodanes with the formation of a metal-stabilized nitrene intermediate has been widely exploited and investigated with respect to the effect of varying (1) the olefinic substrate; (2) the nature of the nitrene source; (3) the alkane- or arenesulfonylimino group or the aryl iodide moiety in [*N*-(alkane/arenesulfonyl)imino]aryliodanes; (4) the transition metal catalyst; (5) the ligand for the complexation of the metal, in particular, the chiral ligand for asymmetric aziridination reactions; and (6) the solvent and other conditions for optimizing the aziridination reaction <2006ACR194, 2005COR657>.

Relative rates of the aziridination of styrene **397** versus a series of *para*-substituted styrenes **398** furnishing the respective aziridines **401** and **402** have been determined using Tp′Cu(C_2H_4) (Tp′ = hydridotris(3,5-dimethyl-1-pyrazolyl)borate) **400** as the copper precatalyst in combination with PhI═NTs **399** as the nitrene source. The experimental data of the aziridination reaction can be fit with a two-term equation of the type $\log(k_X/k_H) = \rho^+\sigma^+ + \rho^*\sigma^*$ (σ^* are Jackson's radical substituent constants) leading to the values $\rho^+ = -0.28 \pm 0.06$ (polar contribution) and $\rho^* = +0.34 \pm 0.13$ (radical contribution). A paramagnetic copper nitrene species **403**, which behaves as an electrophilic nitrogen-centered radical, has been proposed as the intermediate for the aziridination reaction (**Scheme 102**) <1997OM4399>.







	Product ratios [**402**]/[**401**]	
X	*Experimental*	*Calculated*[a]
OMe	2.43	2.33
Me	2.13	1.67
Ph	1.36	1.56
H	1.00	1.00
Cl	1.21	1.07
CF_3	1.02	b
NO_2	1.15	1.08

[a]Calculated using the dual-parameter equation $\log(k_X/k_H = r^+s^+ + r^*s^*$, where $r^+ = -0.28$, $r^* = +0.34$; s^+ are Hammett constants, and s^* are Jackson's constants.
[b]No s* available.

Scheme 102

A detailed study of the aziridination of styrene contrasting the use of PhI=NTs and PhI=NNs as nitrene donors with both the homogeneous catalyst, $Cu(OTf)_2$, and the heterogeneous catalyst, copper-exchanged zeolite Y (CuHY), has been carried out in order to find optimal conditions. The ratio of styrene/nitrene donor significantly affects the yield of the aziridine formed and the enantioselection when a chiral bis(oxazoline) ligand is added to the reaction. In general, a slight excess of the nitrene donor gives the best results (styrene/nitrene donor 1:1.5), and high ee's (≥85%) can be achieved with the heterogeneous catalyst, particularly when PhI=NNs is used as the nitrene donor. Coordinating solvents (acetonitrile, nitromethane) give the highest yields of the aziridine, but with CuHY, high ee's are only obtained with acetonitrile. With respect to the requirements of the structure of the chiral modifier, the heterogeneous catalyst can give high enantioselection for many ligands such as **404** (**Figure 1**).

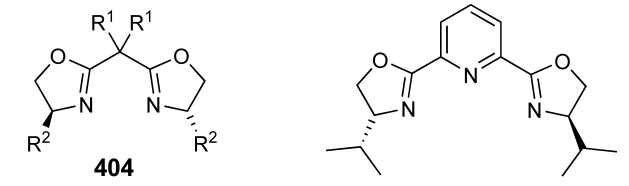
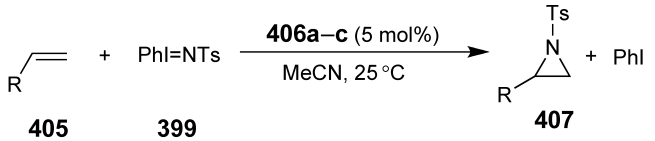
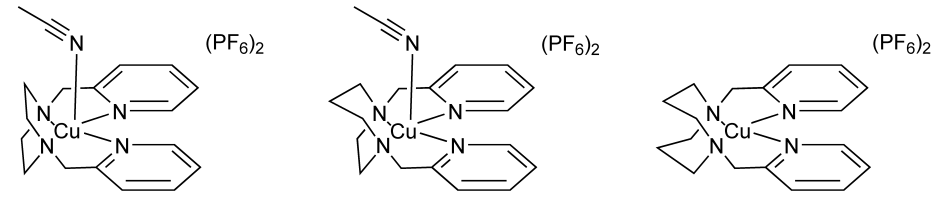


Figure 1

Copper(II) complexes of 2-pyridylmethyl-appended diazacycloalkane ligands **406a–c** are efficient catalysts for the aziridination of alkene **405a** with PhI=NTs **399** (forming aziridine **407**), while only **406a** exhibits significant catalytic nitrene-transfer reactivity with 1-hexene (**Scheme 103**) <2000IC4903>.



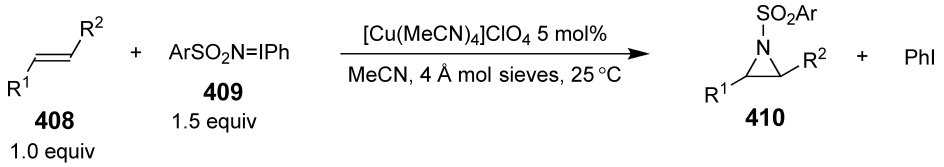
R	*Catalyst* **406**	*Reaction time* (*h*)	**407** (%)
Ph	**a**	8	85
Ph	**b**	8	87
Ph	**c**	8	80
C_4H_9	**a**	36	35
C_4H_9	**b**	24	0
C_4H_9	**c**	24	0



Scheme 103

A series of [*N*-(arenesulfonyl)imino]phenyliodanes **409** have been evaluated for their utility as nitrene precursors for the copper-catalyzed $[Cu(MeCN)_4ClO_4]$ aziridination of various olefins **408**. Best results were obtained with

4-nitro- and 4-methoxy-substituted [*N*-(benzenesulfonyl)imino]phenyliodanes (**409**: Ar = 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$, respectively), both of which were found superior to [*N*-(benzenesulfonyl)imino]phenyliodane (Ar = Ph). Using 1.0 equiv of olefin **408** and 1.5 equiv of the nitrene precursor **409**, the corresponding aziridine products **410** were obtained in good to excellent yields (60–99%) (**Scheme 104**) <1997TL6897>.



R^1	R^2	*Ar*	*Conditions*[a]	**410** (%)
Ph	H	4-$O_2NC_6H_4$	A	99
C_8H_{17}	H	4-$O_2NC_6H_4$	B	70
Bn	H	4-MeC_6H_4	B	48
Bn	H	4-$O_2NC_6H_4$	B	71[b]
Ph	Me	4-$O_2NC_6H_4$	A	97
Ph	CO_2Me	4-MeC_6H_4	A	40
Ph	CO_2Me	4-$O_2NC_6H_4$	A	62
Ph	CO_2Me	4-$MeOC_6H_4$	A	60[b]

[a]Method A: slow addition (3 h) of 1.5 equiv **409**; method B: 1.5 equiv **409** added at once.
[b]Reaction at 0 °C.

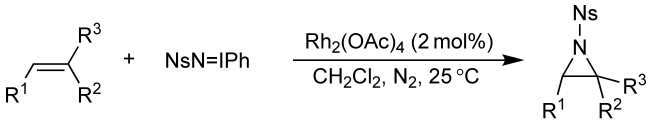
Scheme 104

Rhodium(II)-based catalysts such as $Rh_2(OAc)_4$ have been found to be less efficient in the reaction of styrene with [*N*-(4-toluenesulfonyl)imino]phenyliodane (59% yield), but the reaction proceeds well with [*N*-(4-nitrobenzenesulfonyl)imino]-phenyliodane (NsN=IPh **412**) at room temperature <1996T1543>. The aziridination of (*E*)- and (*Z*)-alkenes with NsN=IPh **412** occurs stereospecifically in some cases as with (*E*)- and (*Z*)-1-propenylbenzene, (*E*)- and (*Z*)-2-hexene affording the corresponding *cis*- and *trans*-2,3-disubstituted *N*-(4-nitrobenzenesulfonyl)aziridines. A mixture of *cis*- and *trans*-aziridines **413** results from the reaction of *cis*-stilbene; the *trans*-aziridine isomer derived from *trans*-stilbene suffers phenyl migration induced by $Rh_2(OAc)_4$ and rearranges to give rise to *N*-(2,2-diphenylvinyl)-4-nitrobenzenesulfonamide (**Scheme 105**) <1996T1543>.

Aziridination of olefins of type **414** using PhI=NTs **399** is efficiently catalyzed by copper(II) acetylacetonate immobilized in ionic liquids such as $bmimBF_4$ or $bmimPF_6$, providing good yields of aziridines **415** at a faster rate than the earlier reported methods and with the additional benefit of easy catalyst/solvent recycling (bmim = 1-butyl-3-methylimidazalium, **Scheme 106**) <2004SL525>.

Nitrene or nitrene precursors such as [*N*-(*p*-toluenesulfonyl)imino]phenyliodane **399** can add to an alkene **416** forming an aziridine **417** and/or can insert into the allylic C–H bond forming an allylamine derivative **418**. Depending on the transition metal catalyst used (in combination with a complexing ligand), the reaction of nonactivated alkenes with [*N*-(*p*-toluenesulfonyl)imino]phenyliodane **399** as the nitrene source results predominantly in allylic amination with aziridination as a side reaction <2005JOM(690)2142>. The reaction has been extensively studied with cyclohexene **416b**, using Co(II) catalysts Co(II) (2*Z*,4*E*,8*E*,10*Z*)-4,9-dimethyl-5,8-diaza-2,4,8,10-dodecatetraene-2,11-diolate (Co(acacen), **420**) and Co(II) tetraphenylporphyrin dianions (Co(TPP), **421**). The reaction conditions (solvent, reaction time, and the ratio TsN=IPh **399**/catalyst) determine the ratio between aziridine **417** and the allylic amination product **418**, which is also formed (**Scheme 107**).

Experimental observations of the aziridination of styrene-type alkenes, catalyzed by $CuPF_6$ in the presence of chiral diimine ligands (such as (1*R*,2*R*,N^1*E*,N^2*E*)-N^1,N^2-bis(2,6-dichlorobenzylidene)cyclohexane-1,2-diamine **425**), have been taken as evidence of the intermediacy of a discrete, monomeric Cu(III)–nitrene complex, (diimine)Cu=NTs **423**. Variation of the steric properties of the aryl group in the oxidant TsN=IAr (Ar = Ph, 2-*t*-Bu-4,5,6-Me_3C_6H) has no effect on the enantioselectivities in forming the aziridination products **424** (**Scheme 108**) <1995JA5889>.

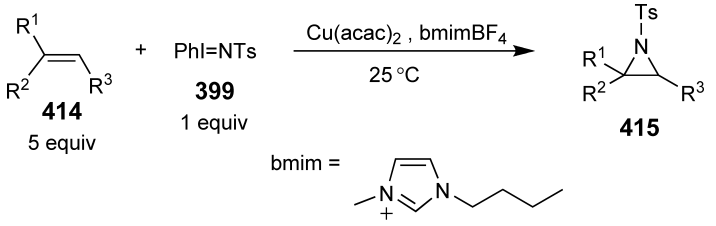


411 **412** **413**

R^1	R^1	R^2	*Time* (*h*)	**413** (%)
Ph	H	H	2.3	85[a]
4-MeC_6H_4	H	H	0.5	76[a]
4-$AcOC_6H_4$	H	H	0.75	82[a]
3-$O_2NC_6H_4$	H	H	0.5	46
C_4H_9	H	H	1.0	63
AcO	H	H	4.0	47
Ph	H	Me	18	68
Ph	Me	H	0.25	82
C_3H_7	H	Me	0.5	27
C_3H_7	Me	H	0.5	54
Ph	H	Ph	36	41[b]
Ph	Ph	H	19	18[c]
H	Ph	Ph	0.2	59[d]

[a]5 mmol **412**.
[b]Rearrangement to *N*-(2,2-diphenylvinyl)-4-nitrobenzenesulfonamide in 36 h, 11%.
[c](*E*/*Z*)-ratio 23:77.
[d]10 mmol **412**.

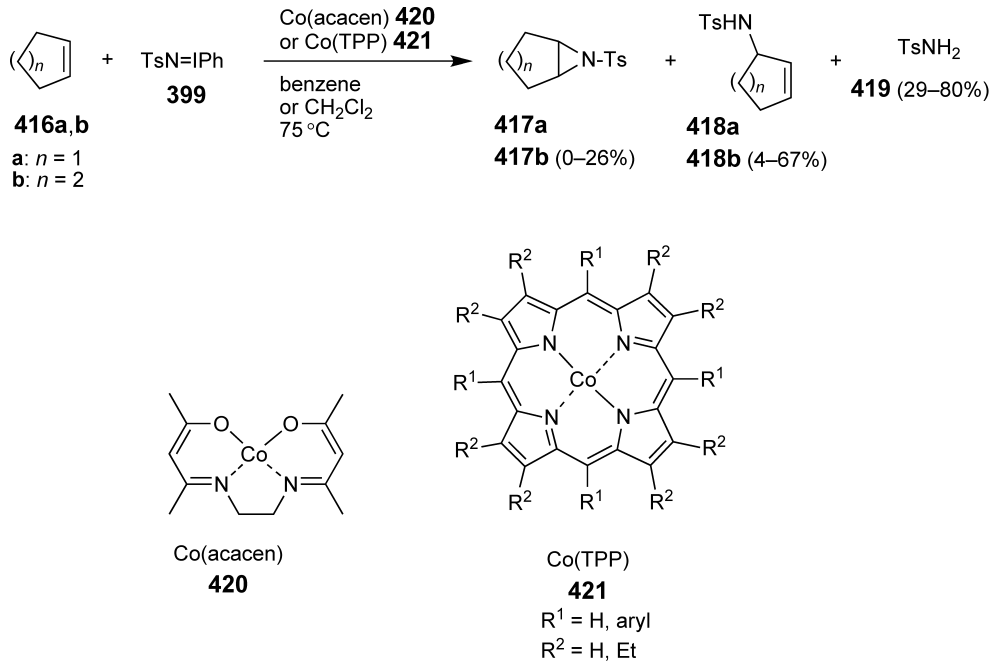
Scheme 105



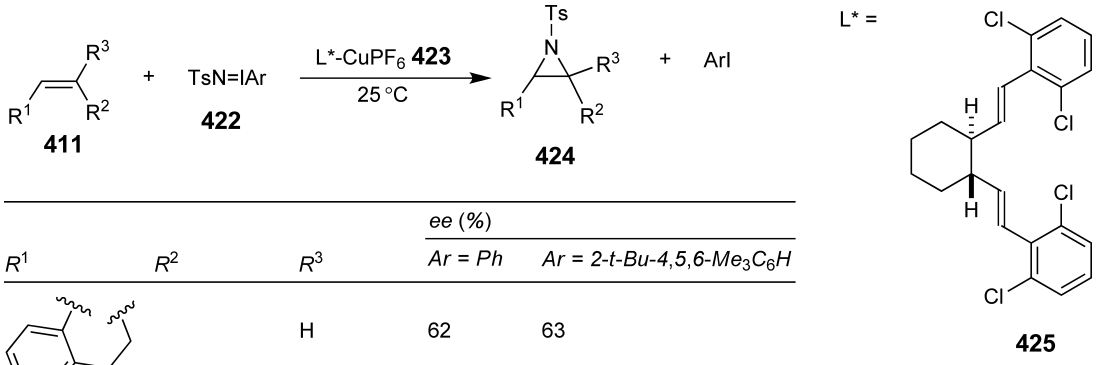
R^1	R^2	R^3	*Reaction time* (*min*)	**415** (%)
Ph	H	H	25	88
Ph	H	H	25	84[a]
Ph	H	H	60	95[b]
Ph	H	Me	10	87
Ph	Me	H	15	78
C_6H_{13}	H	H	10	65
Ph	H	CO_2Me	10	78

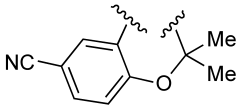
[a]With $bmimPF_6$.
[b]MeCN as solvent.

Scheme 106



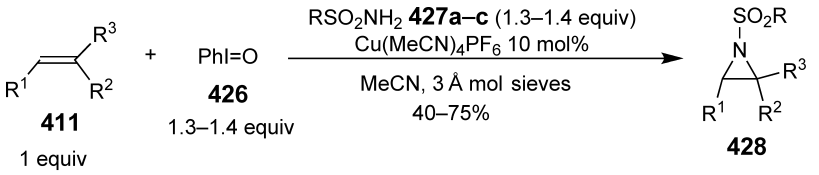
Scheme 107



			ee (%)	
R^1	R^2	R^3	*Ar = Ph*	*Ar = 2-t-Bu-4,5,6-Me$_3$C$_6$H*
		H	62	63
		H	82–85	84
Ph	H	CO_2Me	71	70
Ph	H	H	42	39–43

Scheme 108

A major drawback of the aziridination reaction of olefins is the preparation and isolation of iminoiodanes, some of which have been reported to be unstable and explosive <1997TL6897, 1996CRV1123>. The nitrogen transfer from sulfonamides such as *p*-toluenesulfonamide **427a**, 4-methoxybenzenesulfonamide **427b**, and 2-(trimethylsilyl)ethanesulfonamide ($SesNH_2$, **427c**) has been shown to be mediated by the primary oxygen source iodosylbenzene (PhI=O, **426**); thus, alkenes **411** are converted into aziridines **428** in a one-pot reaction (**Scheme 109**) <2001JA7707>.

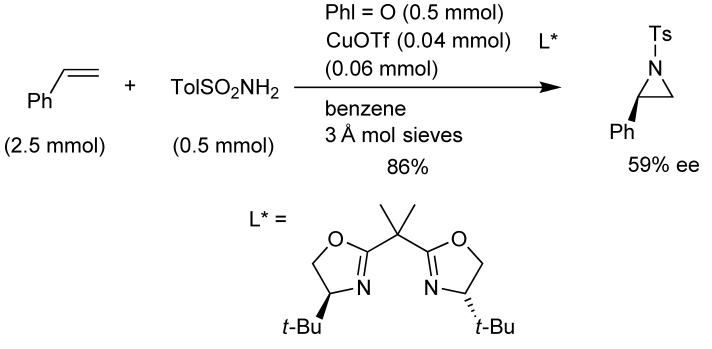


411: R^1, R^2, R^3 = Ph, H, H; H, Me, CO_2Me; Ph, H, CO_2Me; H, H, CO_2Me; Me, Me, CO_2Me; cyclohexene, norbornene, 1,2-dihydronaphthalene

427a: R = 4-MeC_6H_4; **427b**: 4-$MeOC_6H_4$; **427c**: $Me_3SiCH_2CH_2$ (Ses)

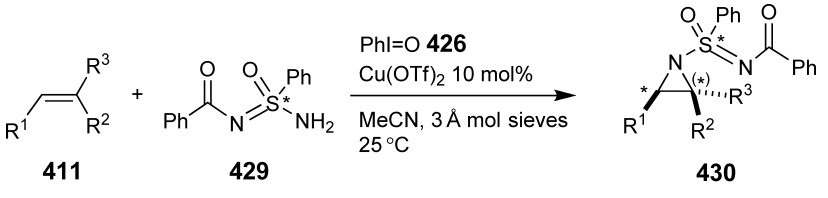
Scheme 109

The asymmetric copper-catalyzed aziridination of styrene with *p*-toluenesulfonamide, iodosylbenzene, and 2,2-bis[(4*S*)-*t*-butyl-1,3-oxazolin-2-yl]propane catalyst (Evans catalyst) provided the aziridine product with an ee comparable to that previously obtained (**Scheme 110**) <2001JA7707>.



Scheme 110

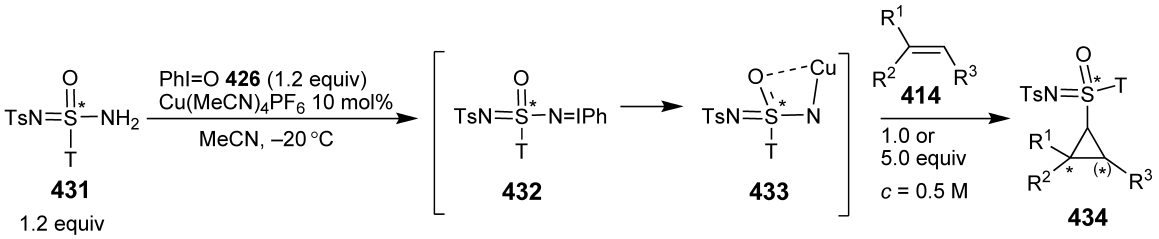
The reaction of *N*-[*S*-(benzoylimino)-*S*-phenylsulfonyl]amide **429** with iodosylbenzene **426** leads efficiently to nitrene intermediates that convert olefins **411** into aziridines **430** in good yields, through a copper(II)-mediated ($Cu(OTf)_2$) reaction. Owing to the stereogenic sulfur atom present in the molecules, the reactions proceed with some degree of diastereoselectivity (**Scheme 111**) <2004OL3573>.



R^1	R^2	R^3	**430** (%)	*d.s.*
Ph	H	H	78	52:48
2-BrC_6H_4	H	H	64	60:40
H	CO_2Me	Me	43	58:42
Me	Me	Me	59	55:45

Scheme 111

The chiral sulfur(VI) reagent, *N*-[[*S*-(*p*-toluenesulfonimido)-*S*-(*p*-tolyl)]sulfonyl]amide **431** upon reaction with iodosylbenzene **426** affords *in situ* the chiral iminoiodane **432**. In the presence of $Cu(MeCN)_4PF_6$ as catalyst, iminoiodane **432** forms the complex **433** that very efficiently transfers the nitrene moiety together with the stereogenic information under stoichiometric conditions to a variety of alkenes **414**: the corresponding aziridines **434** were obtained with diastereoselectivities up to 60% (**Scheme 112**) <2004OL4503>.



T = 4-MeC_6H_4

Ts = 4-$MeC_6H_4SO_2$

			434[a]		**434**[b]	
R^1	R^2	R^3	(%)	*de* (%)	(%)	*de* (%)
CO_2Me	H	H	81	50	93	55
CO_2Me	Me	H	96	41	97	38
CO_2Me	H	Me	35	50	63	60
CO_2Me	Me	Me	92	38	90	40
C_5H_{11}	H	H	60	10	78	10
C_3H_7	H	Me	40	<10	73	<10
H	C_3H_7	Me	57	<10	79	<10
Ph	H	H	63	20	96	<10

[a]With 1.0 equiv of **431**.
[b]With 5.0 equiv of **431**.

Scheme 112

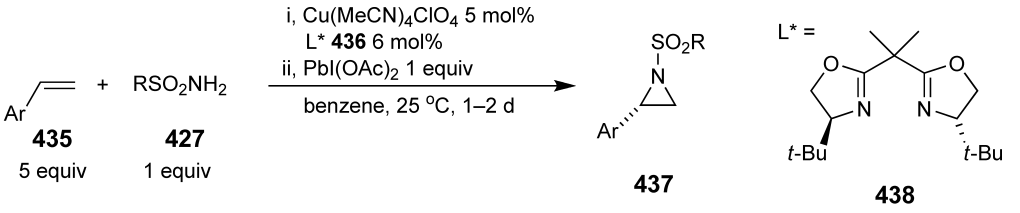
A one-pot procedure designed for the aziridination of a series of styrene derivatives employs commercially available iodobenzene diacetate [$PhI(OAc)_2$] and sulfonamides (**427**, RSO_2NH_2) to generate the nitrene precursors [*N*-(arene/methanesulfonyl)imino]phenyliodanes ($RSO_2N{=}IPh$) *in situ*. The reaction is carried out in the presence of the chiral catalyst $Cu(MeCN)_4ClO_4$–L^* (**436**; $L^* = 2,2$-bis[2-[(4*S*)-*t*-butyl-1,3-oxazolinyl]]propane) to give aziridine **437** (**Scheme 113**) <2004TL3965>.

[*N*-[(Trimethylsilyl)ethanesulfonyl]imino]phenyliodane (SesN=IPh **439**) proved useful for the copper-catalyzed aziridination of alkenes of type **411**. In comparison to TsN=IPh, its isolation is much easier, while their reactivities, that is, yields of aziridine products **440**, are comparable (**Scheme 114**) <1999JOC5304>.

The classical methods for the aziridination of alkenes involve the use of [*N*-(arylsulfonyl)imino]phenyliodinanes (e.g., **442**) as nitrenoid donors, which can be solubilized in organic media by the addition of organic *N*-oxides such as 4-methylmorpholine *N*-oxide or trimethylamine *N*-oxide <1998TL191>. Müller *et al.* <1998JPO597, 1998CJC738> have reported on the rhodium(II)-catalyzed aziridination of olefins using phenyliodonium ylides. The reaction is stereospecific, although yields tend to be modest and a large excess of substrate is usually required. When the chiral rhodium catalyst **444** was used, enantioenriched (~50% ee) products were observed (**Scheme 115**).

1.01.6.2 Transition Metal-Mediated Nitrenoid-Transfer Approach

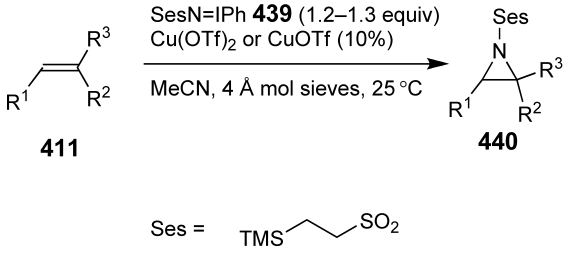
The transition metal-mediated nitrenoid transfer to olefins represents a very concise route to the aziridine structure; very often, however, an excess of the olefinic substrate is required for preparatively useful yields. In this arena, Andersson and co-workers <1997TL6897> have studied the copper-catalyzed aziridination of olefins using [*N*-(arenesulfonyl)imino]phenyliodinanes **446** as nitrene precursors, and have reported on conditions which give good to excellent yields of aziridines **447** without the constraint of having to use an excess of alkene (**Scheme 116**).



		437	
Ar	*R*	(%)	*ee* (%)
Ph	4-MeC_6H_4	75	48
	4-$O_2NC_6H_4$	**94** (91)[a]	**75** (66)[a]
	4-ClC_6H_4	90	52
	Ph	82	50
	4-*t*-BuC_6H_4	75	48
	4-$MeOC_6H_4$	55 (73)[a]	33 (78)[a]
	2-$O_2NC_6H_4$	66	22
	Me	86	36
4-FC_6H_4	4-$O_2NC_6H_4$	**95**	**72**
	4-ClC_6H_4	95	51
	4-MeC_6H_4	84	40
4-$F_3CC_6H_4$	4-$O_2NC_6H_4$	64	51
	4-ClC_6H_4	68	43
	4-MeC_6H_4	43	38
4-MeC_6H_4	4-$O_2NC_6H_4$	78	45
	4-ClC_6H_4	80	43
	4-MeC_6H_4	61	32
3-$O_2NC_6H_4$	4-$O_2NC_6H_4$	82	52
	4-ClC_6H_4	89	48
	4-MeC_6H_4	77	45
3-MeC_6H_4	4-$O_2NC_6H_4$	68	57
	4-ClC_6H_4	78	42
	4-MeC_6H_4	76	37

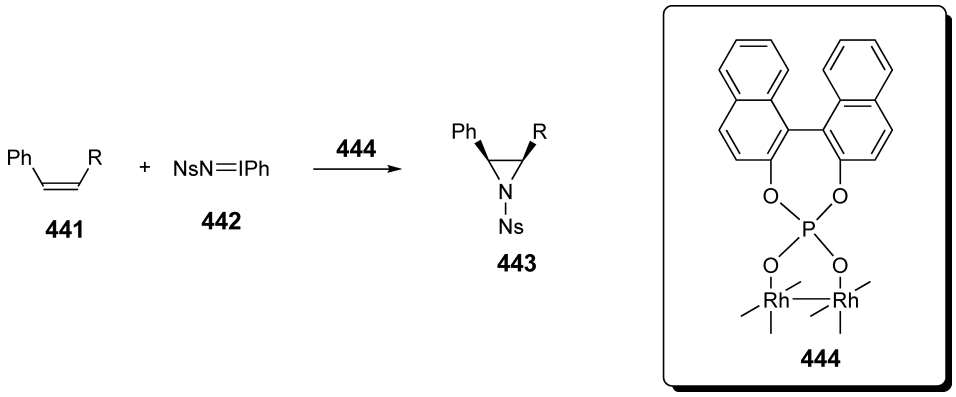
[a]In parentheses: Yield resulting from the two-step procedure employing isolated RSO_2N=IPh with CuOTf as catalyst at 0 °C.

Scheme 113

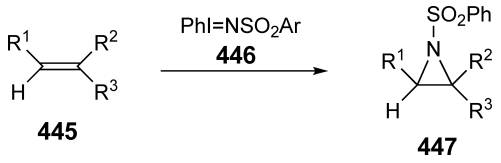


R^1	R^1	R^2	*Cat.*	**440** (%)
Ph	H	H	Cu(II)	58
			Cu(I)	68
Ph	H	CO_2Me	Cu(II)	37
			Cu(I)	39
H	H	CO_2Me	Cu(II)	49
H	Me	CO_2Me	Cu(II)	52
			Cu(I)	60
Me	Me	CO_2Me	Cu(II)	47
H	Ph	CO_2t-Bu	Cu(II)	48
n-C_9H_{19}	H	H	Cu(II)	33
			Cu(I)	43

Scheme 114



Scheme 115



Scheme 116

Jacobsen has studied the asymmetric aziridination of alkenes using (diimine)–copper(I) catalysts **448** (**Figure 2**). The results support the intermediacy of a discrete Cu(III)–nitrene intermediate and thus suggests mechanistic similarity (particularly regarding transition state geometry) to asymmetric cyclopropanation <1995JA5889>.

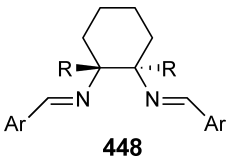
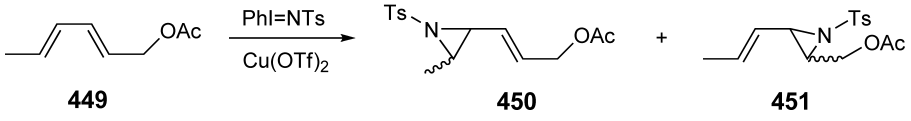


Figure 2

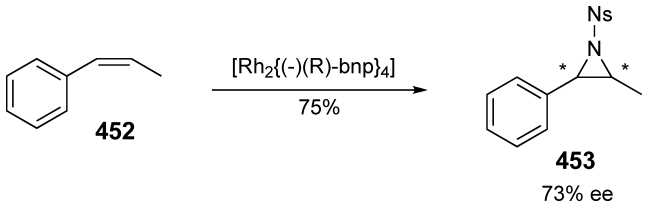
This nitrene-addition approach was used by Knight to synthesize vinyl aziridines from 1,3-dienes using PhI=NTs and a copper catalyst. The more-electron-rich double bond is selectively transformed in most cases. When the electronic difference is negligible, the regioselectivity is then determined by steric hindrance. A mixture of *cis*- and *trans*-isomers is usually obtained (**Scheme 117**) <1995SL949>.



Scheme 117

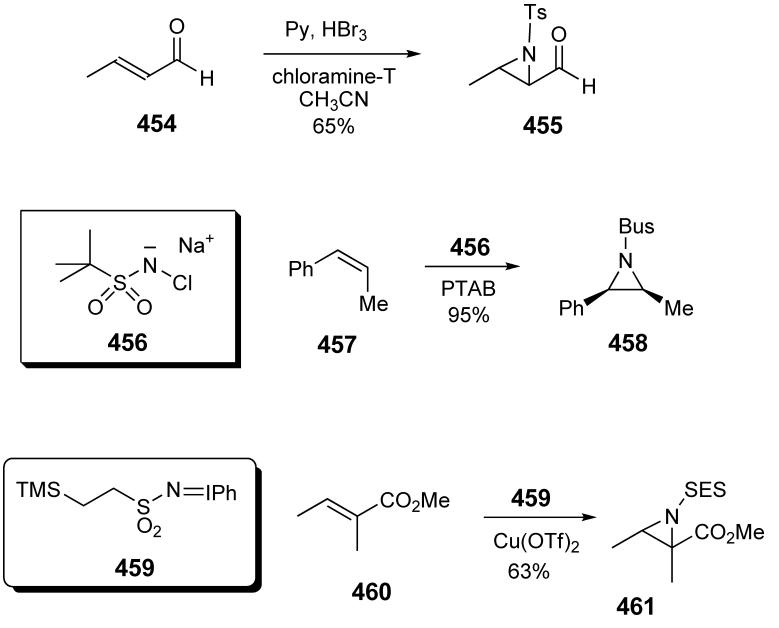
New variants of the (N+C=C) approach continue to be reported. Müller *et al.*, who recently reviewed the field of rhodium(II)-catalyzed aziridinations with [*N*-(*p*-nitrobenzenesulfonyl)imino]phenyliodinane <1996JPO341>, have

explored the application of this technology to asymmetric synthesis. Thus, treatment of *cis*-β-methylstyrene **452** with PhI=NNs and Pirrung's catalyst [Rh_2{(−)(R)-bnp}$_4$] in methylene chloride medium afforded the corresponding aziridine **453** in 75% yield and 73% ee (**Scheme 118**) <1996T1543>.



Scheme 118

Alkenes can be aziridinated using a variety of nitrogen sources. Among the recently reported systems are chloramine-T (*N*-chloro-*N*-sodio-*p*-toluenesulfonamide) with pyridinium hydrobromide perbromide catalyst (e.g., **454** → **455**) <1999OL705>, the *N*-chloramine salt of *t*-butylsulfonamide **456**, which serves as both nitrogen source and terminal oxidant, in the presence of phenyltrimethylammonium tribromide (PTAB) <1999OL783>, and *N*-[2-(trimethylsilyl)ethanesulfonyl]iminophenyliodinane **459** (**Scheme 119**) <1999JOC5304>. The last example is particularly interesting, in as much as it represents the first *N*-alkylsulfonyl derivative used for such purposes. The trimethylsilylethanesulfonyl (SES) group has the advantage of being easily removed under conditions which are amenable to substrates with sensitive functionality.

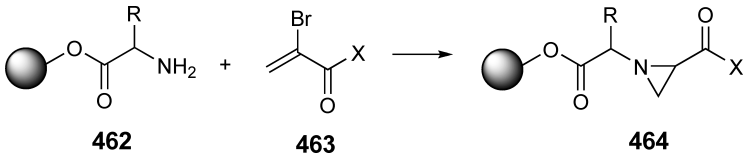


Scheme 119

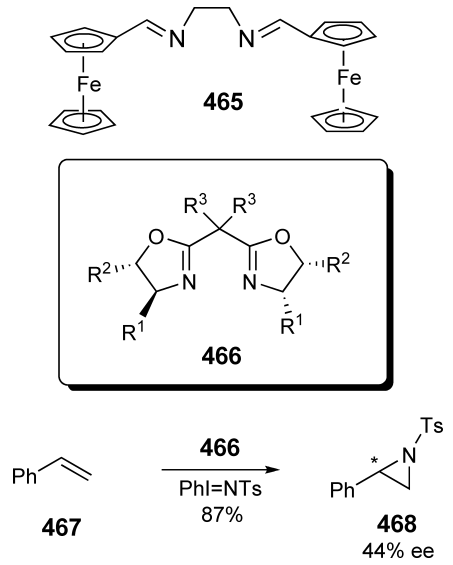
In the realm of heterogeneous catalysis, a copper-exchanged zeolite (CuHY) modified with bis-oxazoline was found to exhibit modest asymmetric induction in the aziridination of alkenes using [*N*-(*p*-tolylsulfonyl)imino]phenyliodinane (PHI=NTs) as the nitrene donor <1999J(P2)1043>. Oligopeptides and amino acids containing an aziridine 2-carboxylate group have been prepared using a solid-phase version of the Gabriel–Cromwell reaction (i.e., **462** → **464**) (**Scheme 120**) <1999TL6503>.

There are reports on the use of a Cu(I) complex of ferrocenyldiimine **465** to facilitate nitrene transfer to olefins <1998SL617>. Of particular interest for industrial applications, these reactions can also be efficiently catalyzed by

copper-exchanged zeolite (CuHY) in acetonitrile. Some degree of asymmetric induction has been observed under these conditions using chiral bis(oxazoline) modifiers (e.g., **466**). For example, styrene **467** was converted to the corresponding aziridine **468** in 82% yield and 44% ee. The solid-supported catalysts can be easily removed from the reaction mixture, washed, and reused without detrimental effect to catalytic or enantioinductive activity (**Scheme 121**) <1998CC1601>.

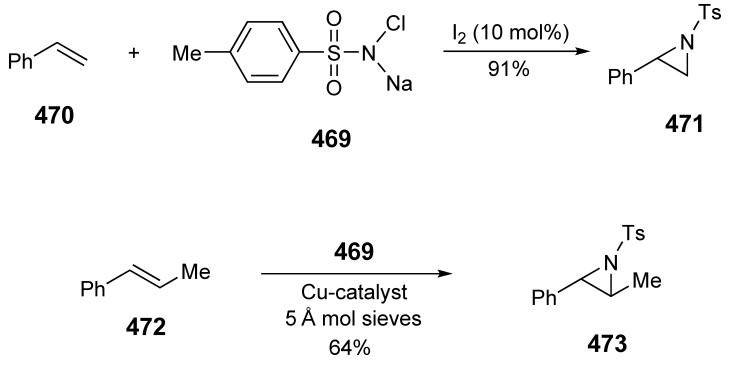


Scheme 120



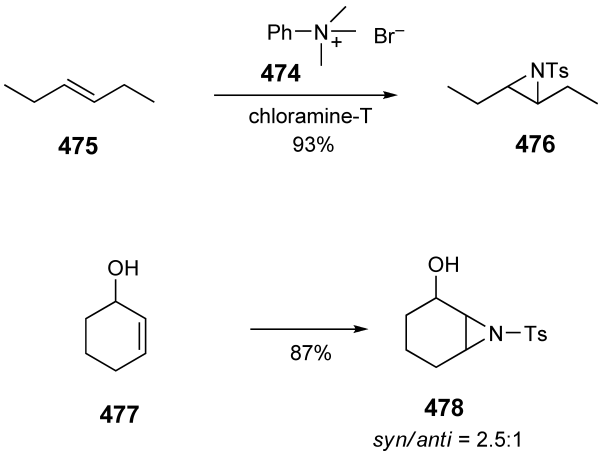
Scheme 121

In the arena of alternative nitrene sources, a flurry of activity has centered around the use of the readily available chloramine-T **469**. Komatsu and co-workers have reported on the successful aziridination of alkenes using **469**, catalyzed either by substoichiometric amounts of iodine (e.g., **470** → **471**) <1998T13485> or a combination of 5% cuprous chloride and 5 Å powdered molecular sieves (e.g., **472** → **473**) <1998TL309>. In certain cases, better yields are obtained using the bromo analog, presumably due to the more facile formation of the copper nitrenoid complex (**Scheme 122**) <1998TL4715>.



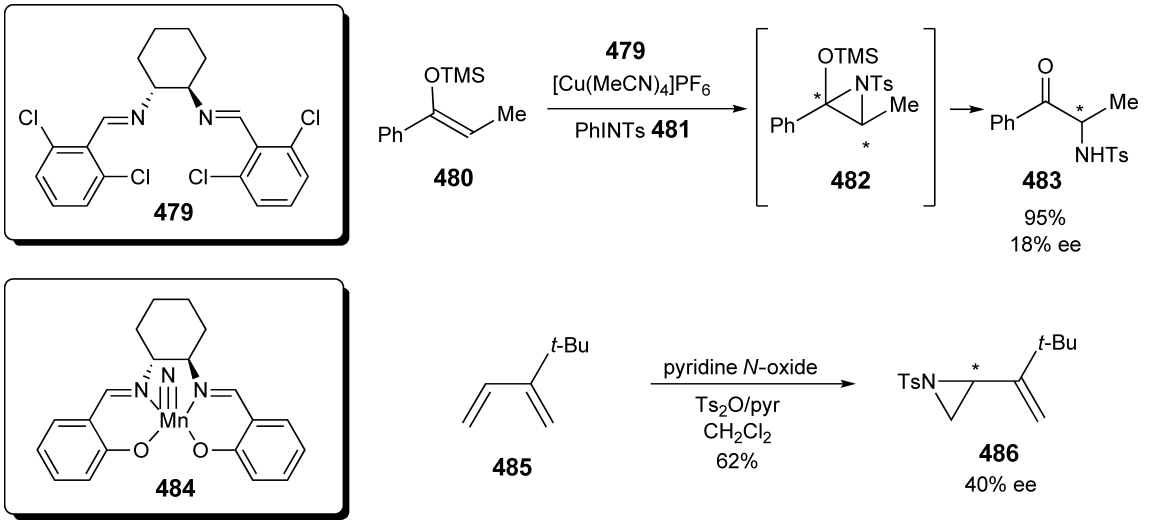
Scheme 122

Sharpless and co-workers <1998JA6844> developed a remarkably efficient aziridination system using chloramine-T with PTAB **474** as the catalyst. This combination provides good to excellent yields of aziridines across a wide range of olefin classes, from simple internal alkenes (e.g., **475** → **476**, 93% yield) to cyclic allylic alcohols (e.g., **477** → **478**, 87% yield) (**Scheme 123**). In the latter case, a slight *syn*-preference (2.5:1) was observed, presumably due to coordination of the aziridinating agent with the hydroxyl group in the transition state.



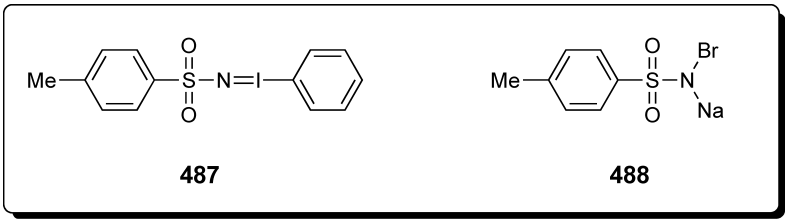
Scheme 123

Cyclic and acyclic enol derivatives **480** can be asymmetrically aziridinated with (*N*-tosylimino)iodobenzene **481** using a chiral copper catalyst prepared *in situ* from $[Cu(MeCN)_4]PF_6$ and the optically active ligand **479**. Collapse of the aminal (i.e., **482**) leads to the formation of enantiomerically enriched α-amino carbonyl compounds **483**, although ee's to date are modest <2000EJO557>. Similarly, dienes can be selectively aziridinated using the chiral Mn–salen complex **484** to give vinyl aziridines **486** in scalemic form (**Scheme 124**) <2000TL7089>.

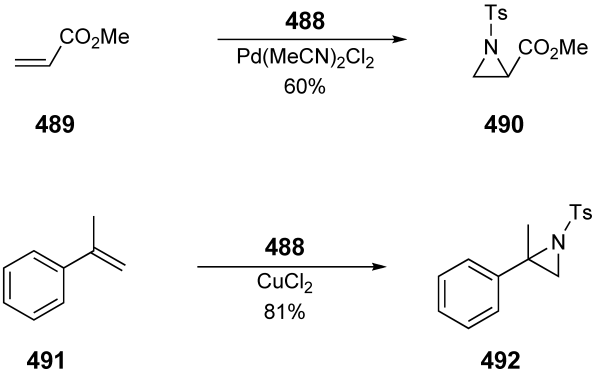


Scheme 124

Two of the more frequently employed nitrene donors correspond to [*N*-(*p*-tolylsulfonyl)imino)]phenyliodinane (PhI=Ts, **487**) and bromamine-T **488**. The latter reactions can be catalyzed by palladium(II) reagents (i.e., **489** → **490**) <2001CC405>, or with a variety of more common transition metals with the assistance of microwave radiation (i.e., **491** → **492**) <2001JOC30>. Similarly, the nitrene-transfer reaction from **487** is facilitated by a variety of catalysts, including methyltrioxorhenium (MTO) <2001CC235>, the tri(pyrazolyl)borate–copper(I) complex <2001OL1423>, and tetrakis(acetonitrile)copper(I) hexafluorophosphate (**Scheme 125**) <2001JA7705>. In the latter case, the reaction can be carried out using a sulfonamide and the primary oxidant, iodosylbenzene, whereby the actual nitrene-transfer reagent is presumed to be formed *in situ*. In all cases, acetonitrile appears to be the solvent of choice.



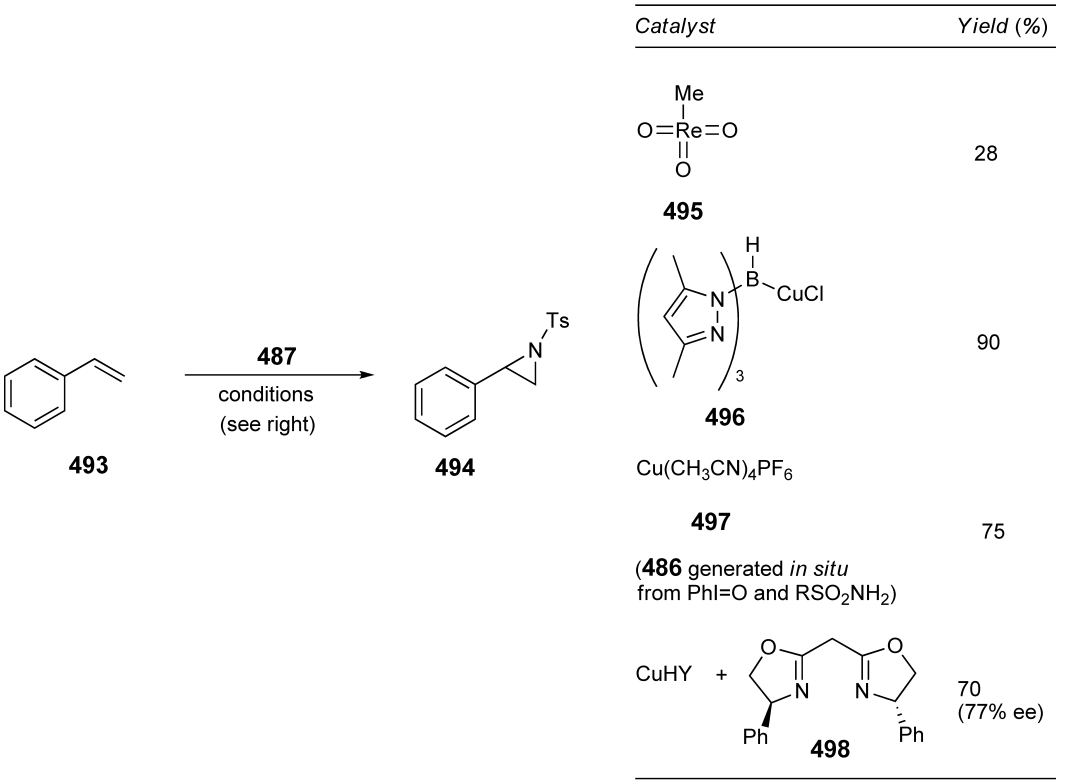
487 **488**



Scheme 125

An interesting asymmetric variant of this methodology has been reported, which employs an immobilized catalyst of Cu^{2+} ion exchanged into zeolite H-Y (CuHY) modified by the chiral bis(oxazoline) **498**. Using nitrene donor **487**, this catalyst system led to the chiral aziridination of styrene **493** in 70% yield and 77% ee, a marked improvement of enantioselectivity compared to the same reaction using the homogeneous catalyst $Cu(OTf)_2$ (28% ee). The optical yield could be further increased by using the *p*-nitrophenyl variant of the nitrene donor, PhI=NNs (82% ee) (**Scheme 126**) <2001J(P2)1714>.

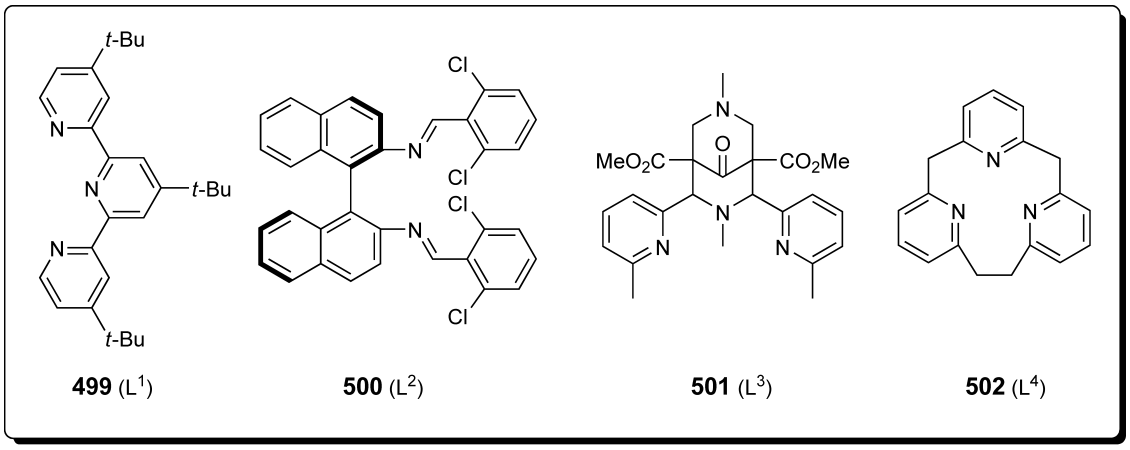
[*N*-9-*p*-Tosyl)imino]phenyliodinane (PhI=NTs), in the presence of some transition metal catalyst, is frequently used as a nitrenoid carrier. Effective catalysts show remarkable diversity, both in structure of the ligands and the metal centers to which they are coordinated. For example, the tridentate *t*-Bu_3tpy ligand **498** forms a 2:2 complex with silver(I) to provide a novel soluble disilver catalyst which exhibits well-controlled oxidation reactivity as seen in the aziridination of *trans*-methylstyrene **503** <2003JA16202>. The tetradentate pyridyl ligand **501** was found to provide the most efficient catalyst with copper(I) ion in the aziridination of styrene **505**, but subtle changes to the ligand structure resulted in striking differences in the properties of the resultant catalyst <2003EJI1711>. The macrocyclic pyridinophane **502** gives rise to an interesting conformationally strained 'capped' catalyst that is particularly reactive, converting cyclooctene **507** to the corresponding aziridine **508** in near-quantitative yield <2003OL2591>. The chiral copper(I) complexes derived from binaphthyldiimine **500** (BINIM-TC) are effective in the asymmetric aziridination of 3-aryl-2-propen-1-ones (e.g., **509**) with excellent ee (**Scheme 127**) <2003BCJ189>.



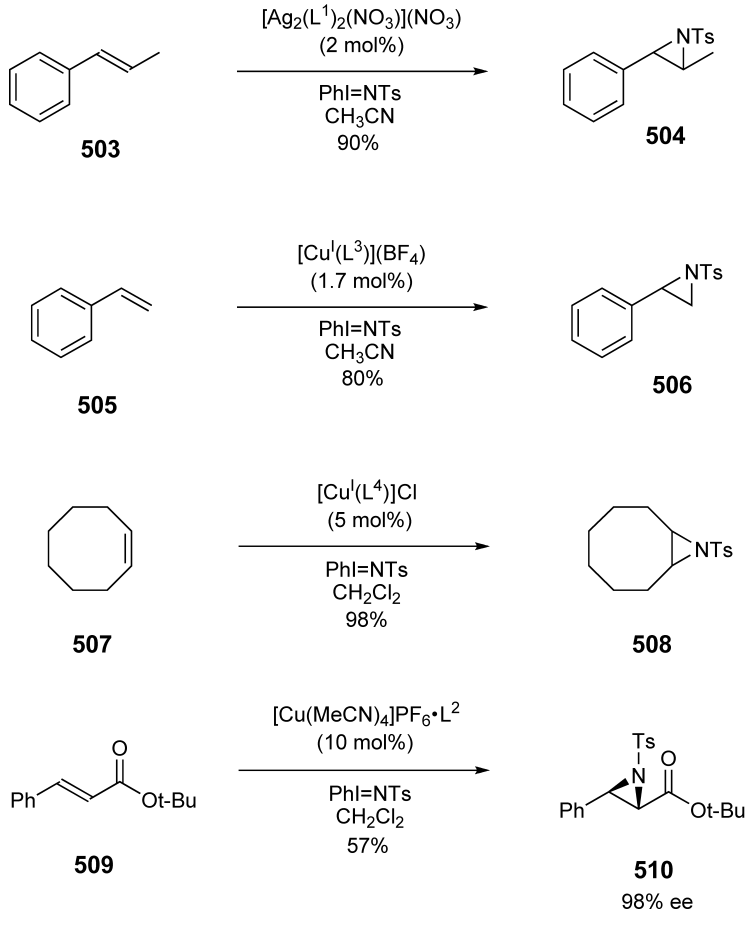
Scheme 126

Other interesting catalyst systems include copper(II) acetylacetonate (acac) immobilized in ionic liquids such as 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (bmimBF_4), which facilitates catalyst recycling and also appears to accelerate the reaction. Thus, *trans*-methylstyrene **511** was converted to the corresponding tosyl aziridine **512** within 10 min using (tosylimino)phenyliodinane as the nitrogen donor <2004SL525>. Bromamine T **515** is also a convenient, stable, and commercially available nitrene precursor. The perfluoroaryl iron porphyrin catalyst **513** is effective in promoting aziridination of a wide spectrum of alkenes in fair to good yields, as illustrated by the conversion of styrene to the corresponding *N*-tosyl aziridine **516**, which is believed to proceed through a mechanism involving an iron–nitrene intermediate <2004OL1907>. A fluorinated aryl ligand is also at the heart of a chiral ruthenium(salen) catalyst **517** designed for the purpose of effecting enantioselective aziridination of olefins using sulfonyl azides as nitrene precursors. Thus, *p*-bromostyrene **518** provides the corresponding aziridine **519** in the presence of tosyl azide and catalyst **517**. Enantioselectivities can reach as high as 99%, and the protocol also works well when tosyl azide is substituted with nosyl azide (**Scheme 128**) <2004CC2060>.

The use of the rhodium catalyst, $Rh_2(cap)_4$, $TsNH_2$, and NBS provides a number of aziridines in good to excellent yields <2005OL2787>. Another rhodium catalyst, $Rh_2(pfm)_4$ (pfm = perfluorobutyramide), has been shown to catalyze the aziridination of olefins using $TsNH_2$ and $PhI(OAc)_2$ (**Scheme 129**) <2005TL4031>. An advantage of the $Rh_2(pfm)_4$ catalyst system is the reported ability to use a variety of sulfonamides (e.g., nosyl, trichloroethoxysulfonyl) in the aziridination reaction. A cobalt porphyrin catalyst system that uses bromamine-T as the nitrogen source provides excellent yields of aziridines <2005OL3191>. A simple copper complex has been shown to catalyze aziridination as well <2005JOC4833>. This reaction system uses PhINTs as the nitrogen source and requires a



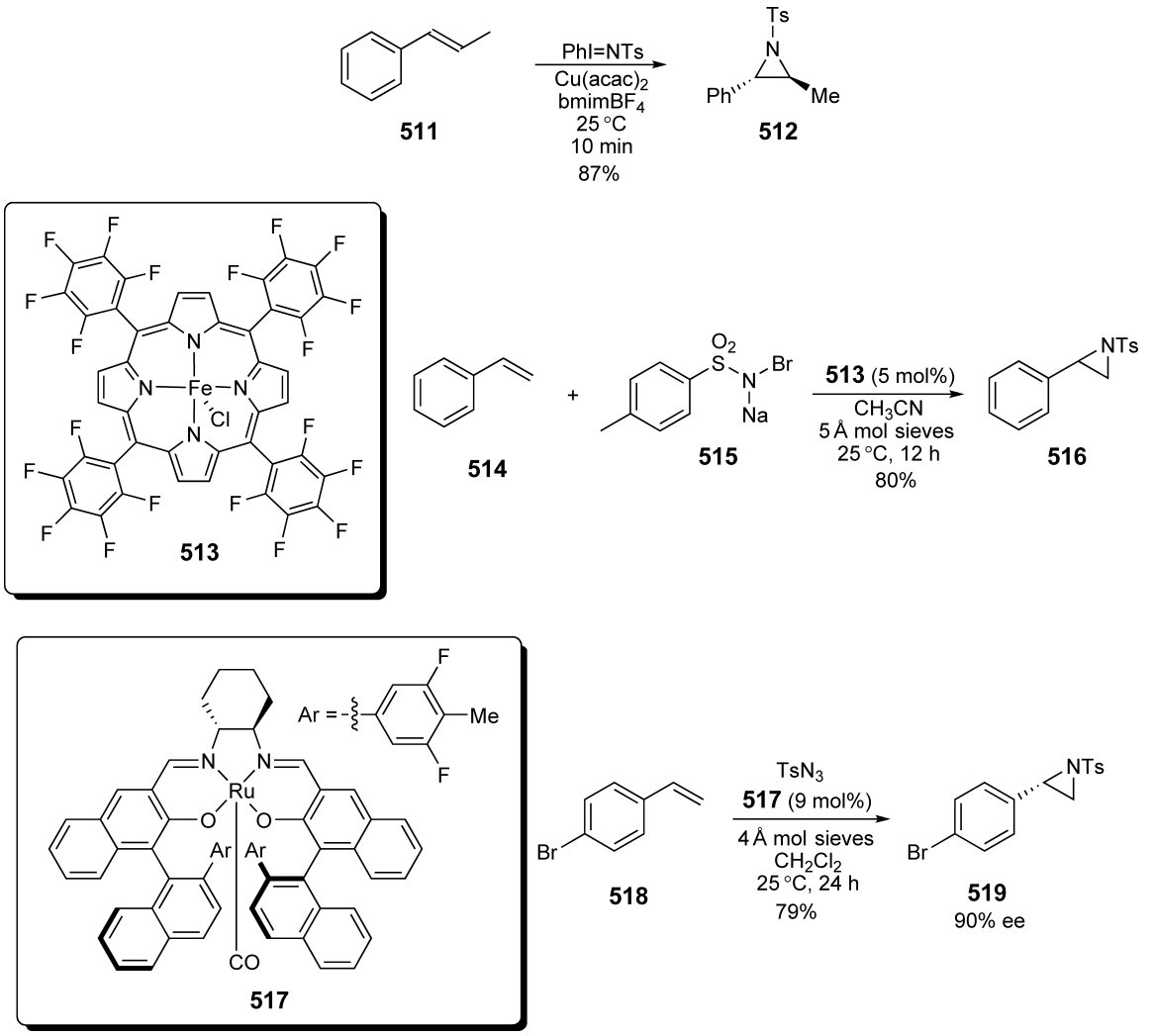
499 (L^1) **500** (L^2) **501** (L^3) **502** (L^4)



Scheme 127

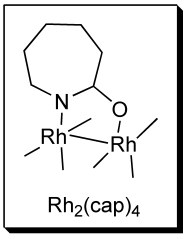
borate, $NaBAr^F{}_4$, to remove the anionic ligands creating a coordinatively unsaturated cationic copper species. A key feature of all of these methods is that the olefinic substrate is the limiting reagent. This is an important feature of being able to use these methods in synthetically significant settings.

Other reagents are also employed as nitrene precursors, primarily in an effort to avoid the practical problems associated with PhI═NTs <2001TL8089>, such as expense of the reagent and the generation of iodobenzene as a



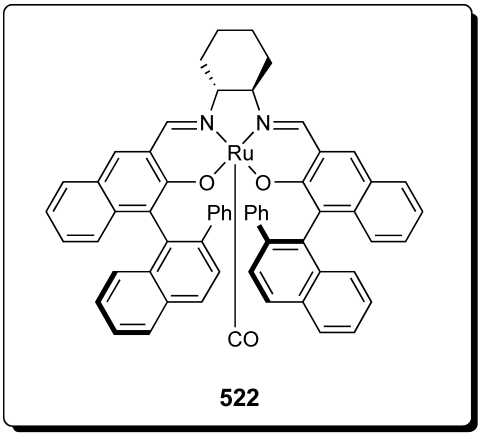
Scheme 128

Catalyst	*Yield*
1 mol% $Rh_2(cap)_4$, NBS, $TsNH_2$	R^1 = Ph; R^2 = H (77%)
	R^1 = *n*-C_4H_9; R^2 = H (77%)
1 mol% $Rh_2(pfm)_4$, $PhI(OAc)_2$, $TsNH_2$	R^1 = Ph; R^2 = H (73%)
	R^1 = *n*-C_3H_7; R^2 = CH_3 (44%)
5 mol% Co(TDClPP), bromamine-T	R^1 = Ph; R^2 = H (83%)
	R^1 = *n*-C_7H_{15}; R^2 = H (56%)
5 mol% $(py)_2CuCl_2$, $NaBAr^F{}_4$, PhINTs	R^1 = Ph; R^2 = H (97%)
	R^1 = *n*-C_4H_9; R^2 = H (49%)

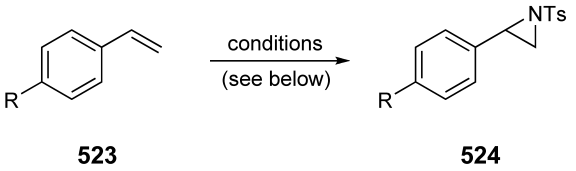


Scheme 129

by-product. For example, tosyl azide has been used in combination with the chiral ruthenium(salen) catalyst **522** to effect the enantioselective aziridination of terminal alkynes with very good ee's <2003CL354>. Another alternative source of latent nitrene is *N*-iodo-*N*-potassio-*p*-toluenesulfonamide (TsN·KI), a stable crystalline solid obtained from the treatment of toluenesulfonamide with iodine in the presence of potassium hydroxide. When used in combination with copper(I) chloride as a catalyst, simple alkenes undergo aziridination in fair to good yields <2003TL575>. Chloramine-T can also be used as a source of nitrogen in the presence of NBS; however, here the mechanism is not believed to proceed through a nitrene species, but rather by initial bromonium ion formation from the alkene, which undergoes subsequent nucleophilic attack by chloramine-T (**Scheme 130**) <2003TL989>.



522



523 **524**

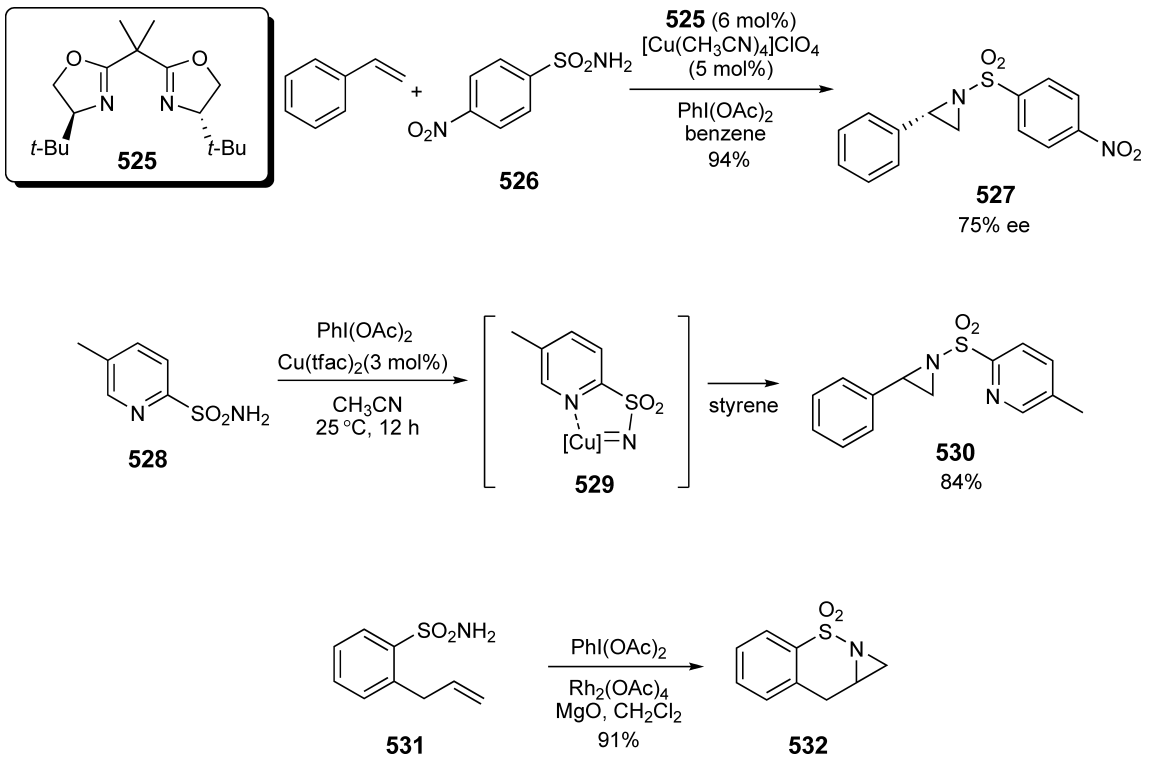
R	*Catalyst*	*Conditions*	*Yield* (%)	*ee* (%)
H	**134** (2 mol%)	TsN_3, CH_2Cl_2	71	87
Me	CuCl (5 mol%)	TsN•KI, CH_3CN	75	*rac*
$ClCH_2$-	NBS (20 mol%)	Chloramine-T, CH_3CN	67	*rac*

Scheme 130

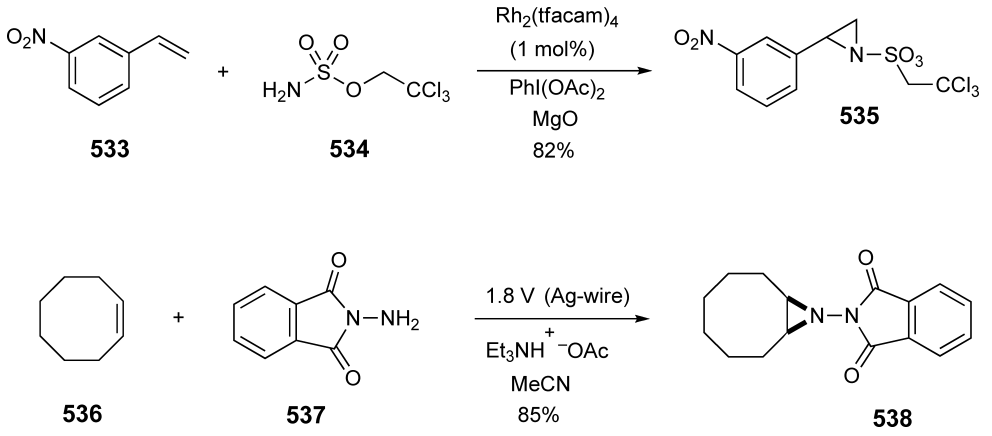
Sulfonamides have been found to be convenient nitrene precursors, which can be converted using commercially available iodobenzene diacetate in the presence of various transition metal catalysts. A copper(I) catalyst derived from the Evans chiral bis(oxazoline) ligand **525** was found to promote the high-yielding aziridination of styrene with good enantioselectivity <2004TL3965>. Chang and co-workers have developed a copper-catalyzed variant that requires no external ligand. Instead, a pyridyl nitrogen onboard the sulfonamide moiety serves as an internal ligand (i.e., **529**), which in turn increases the efficiency of the aziridination <2004OL4109>. Several unsaturated sulfonamides (e.g., **531**) were shown to undergo a very facile intramolecular aziridination in the presence of a rhodium catalyst to provide tricyclic aziridines (e.g., **532**) (**Scheme 131**) <2004JOC6377>.

DuBois and Guthikonda have developed a broadly applicable aziridination of alkenes using a sulfamate ester (e.g., **534**), a rhodium carboxamide catalyst, and iodosylbenzene as a terminal oxidant <2002JA13672>. An intriguing electrochemical approach has also been reported using *N*-aminophthalimide **537** as the nitrogen donor (**Scheme 132**) <2002JA530>.

N-Aminophthalimide **537** can also be added to olefins in an asymmetric fashion. Thus, reaction of *N*-enoyl oxazolidinone **541** with **537** and lead tetraacetate in the presence of the camphor-derived chiral ligand **539** provides aziridine **542** in 83% yield and 95% ee <2002OL1107>. Other useful chiral ligands include imine **540**, derived from the condensation of 2,2′-diamino-6,6′-dimethylbiphenyl with 2,6-dichlorobenzaldehyde. The corresponding



Scheme 131

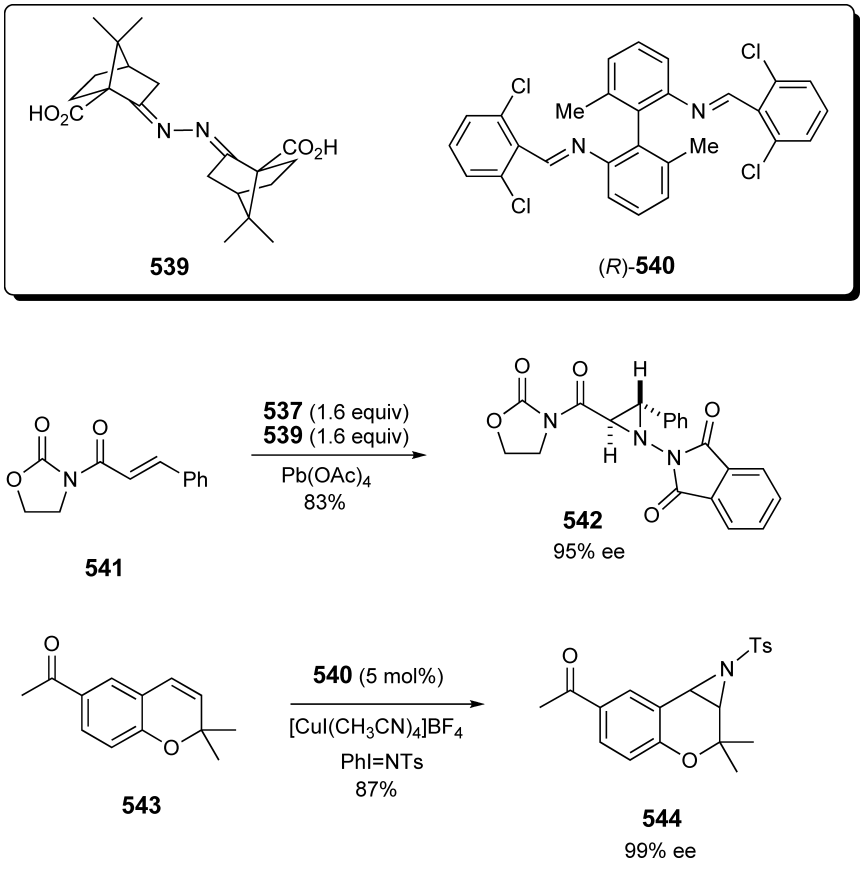


Scheme 132

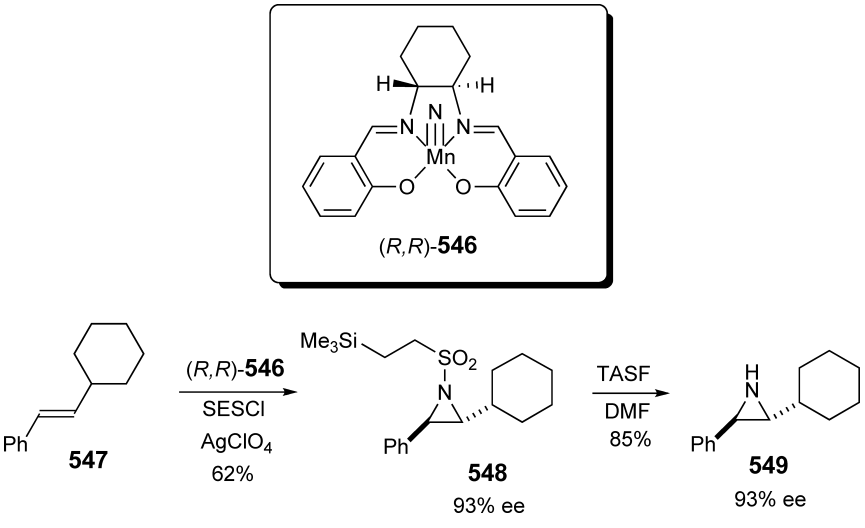
monometallic Cu(I) complex was found to be very efficient in chiral nitrogen transfer onto chromene derivative **543** using (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane (PhI=NTs) to provide aziridine **544** in 87% yield and 99% ee (**Scheme 133**) <2002JOC3450>.

The chiral nitridomanganese complex **546** represents a novel self-contained asymmetric nitrogen-transfer reagent which has been used to convert alkenes to scalemic aziridines directly, although a stoichiometric amount of transfer reagent is required. This protocol makes use of *N*-2-(trimethylsilyl)ethanesulfonyl chloride (SESCl) as an activator, providing *N*-SES-aziridines that are easily deprotected under mild conditions using tris(dimethylamino)sulfonium

difluorotrimethylsilicate (TASF) to give NH-aziridines in good yield. The enantioselectivity can be quite high, especially with *trans*-olefins bearing sterically bulky substituents, as is the case with the cyclohexyl stilbene derivative **547**. However, terminal and *cis*-alkenes tend to be less amenable to chiral induction (**Scheme 134**) <2002JOC2101>.

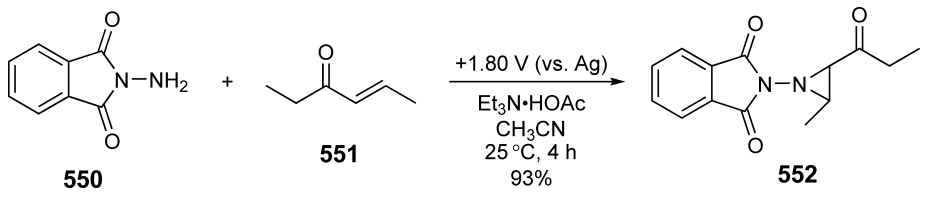


Scheme 133



Scheme 134

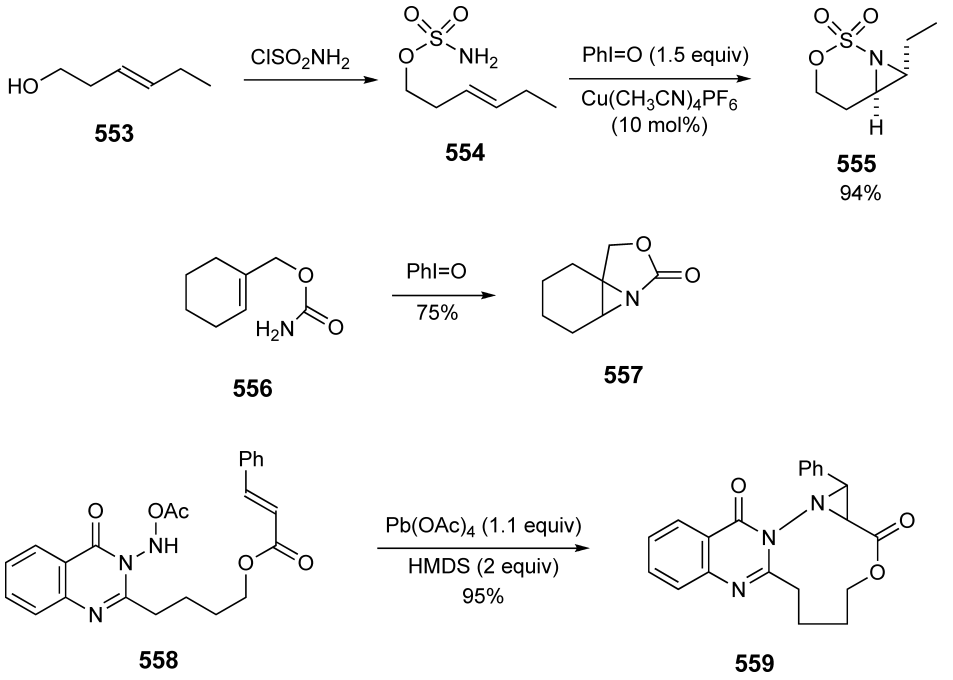
An intriguing electrochemical aziridination is based on the selective anodic oxidation of *N*-aminophthalimide (**550**, oxidation potential +1.60 V) in the presence of olefins. Thus, *trans*-hex-4-en-3-one **551** is converted to the corresponding aziridine **552** in acetonitrile solution using a platinum electrode at a constant potential of +1.80 V (**Scheme 135**). The reaction mixture is buffered using triethylammonium acetate, since the cathodic process reduces proton to hydrogen gas. The use of platinum at the anode is critical, as graphite electrodes yielded no aziridination products <2004PAC603>.



550 **551** **552**

Scheme 135

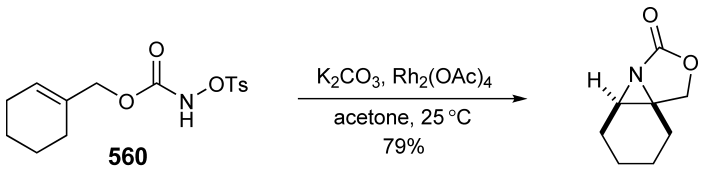
Some interesting intramolecular variants have been reported. For example, homoallylic alcohols (e.g., **553**) can be treated with sulfamoyl chloride to form the corresponding sulfamates **554**, which then engage in a direct intramolecular copper-catalyzed aziridination mediated by iodosylbenzene <2002OL2481>. A carbamate tether is also effective in delivering the nitrene center to the olefin, as is the case with the cyclohexenyl derivative **556**, which spontaneously cyclizes in the presence of iodosylbenzene <2002OL2137>. The acetoxyaminoquinazolinone **558** is converted to the lactone **559** via intramolecular aziridination upon treatment with lead tetraacetate and hexamethyldisilazane (HMDS) (**Scheme 136**) <2002TL2083>.



553 **554** **555** **556** **557** **558** **559**

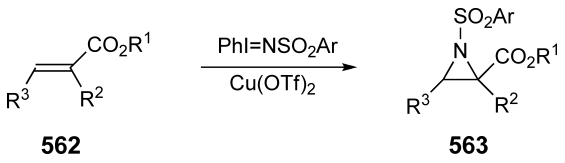
Scheme 136

A rhodium-catalyzed route to bicyclic aziridines **561** from *N*-tosyloxycarbamates has been reported (**Scheme 137**) <2005JA14198>. Several olefins were tested in this intramolecular process with yields ranging between 62% and 79%.



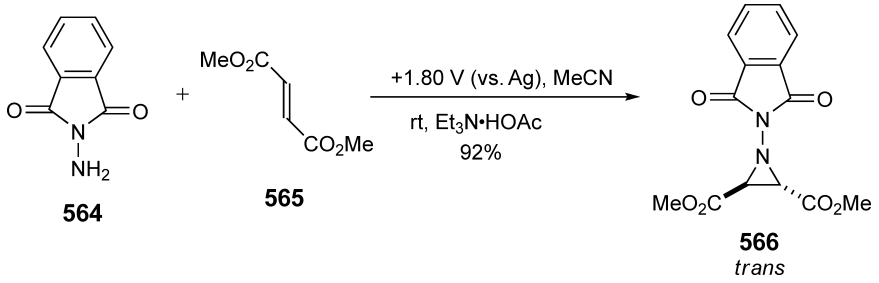
Scheme 137

In the realm of electron-deficient alkenes, 2-substituted acrylates and cinnamates such as **562** can be converted to aziridines **563** by the Evans aziridination procedure. This protocol involves using *N*-(*p*-tolylsulfonyl)iminophenyliodinane in the presence of a catalytic amount of copper salt (**Scheme 138**). Yields are variable, but can be as high as 72% <1998TL5739>.



Scheme 138

The use of *N*-aminophthalimide as a nitrogen source in aziridination reactions has been examined in some detail. One of the problems associated with *N*-aminophthalimide as a nitrogen source is the need for a strong oxidant. The use of electrochemical catalysis with *N*-aminophthalimide has proven to be an effective and mild route for aziridination (**Scheme 139**) <2005JOC932>. Both electron-rich and electron-poor substrates worked well in this reaction.

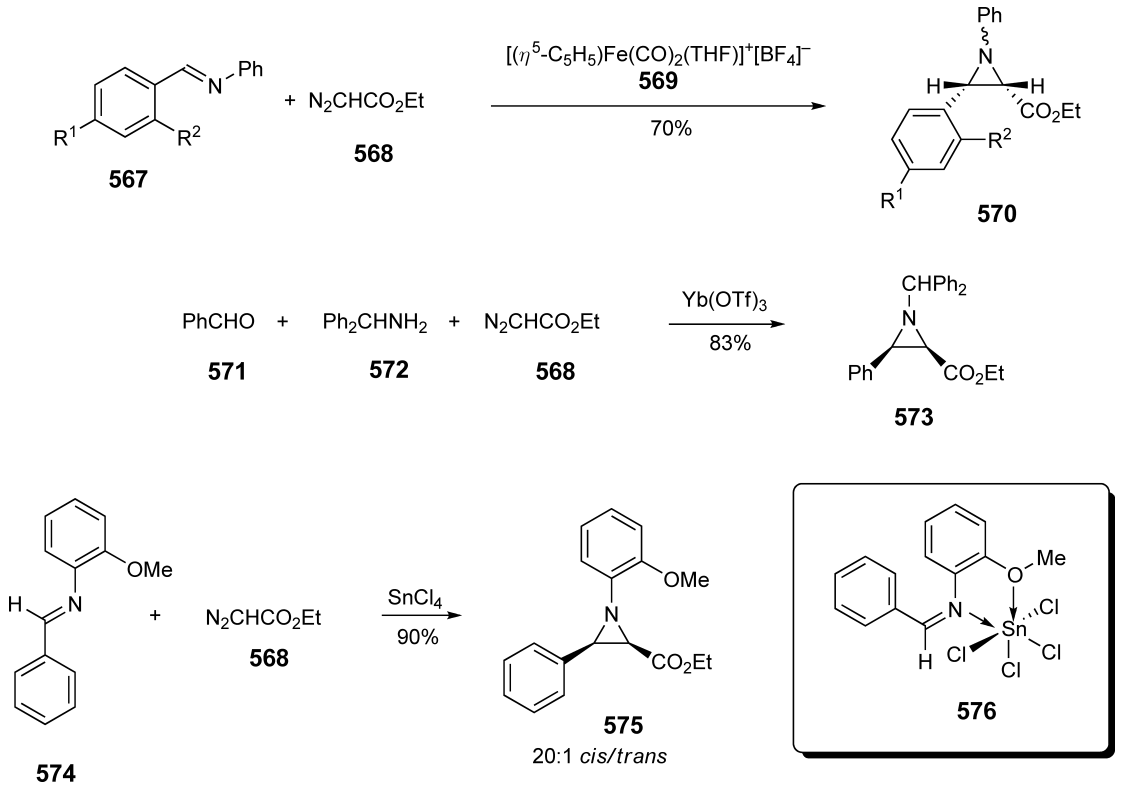


Scheme 139

1.01.6.3 Methylidation of Imines

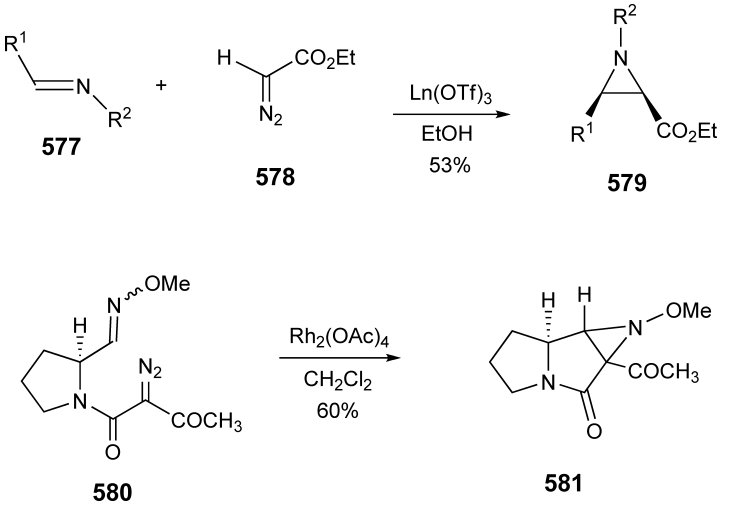
1.01.6.3.1 Preparation of aziridines by reaction of diazo compounds with imines

Another major route used for the preparation of aziridines is the formal addition of carbenoids across an imine π-bond [C+C═N]. The carbon fragment is typically provided by reagents such as ethyl diazoacetate **568**. The reaction can proceed under the influence of various catalysts, such as the iron Lewis acid **569**, which provides predominantly the *cis*-aziridine (e.g., **570**) <1998JOC6839>. It was also found that a mixture of ethyl diazoacetate and the appropriate aldehyde and primary amine (i.e., **571** and **572**) in the presence of catalytic ytterbium triflate leads to the efficient generation of *cis*-aziridines **573** in a one-pot process <1998CL685>. The analogous tin-catalyzed aziridination of imines (i.e., **574** → **575**) has also been investigated. The mechanistic pathway is believed to proceed by nucleophilic attack of ethyl diazoacetate onto the imine, whose π-bond is activated by coordination with the catalyst. This rationale is supported by the isolation of the imine–Lewis acid intermediate **576**, which has been fully characterized by X-ray diffraction studies (**Scheme 140**) <1998J(P2)1347>.



Scheme 140

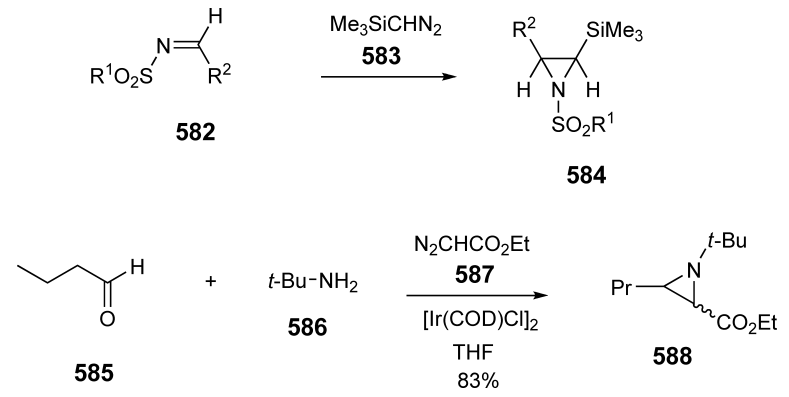
Carboxylate derivatives **579** can be prepared through the lanthanide-catalyzed reaction of imines with diazo compounds, such as ethyl diazoacetate (EDA). In this protocol, *N*-benzyl aryl aldimines and imines derived from aromatic amines and hindered aliphatic aldehydes are appropriate substrates <1999T12929>. An intramolecular variant of this reaction (e.g., **580** → **581**) has also been reported (**Scheme 141**) <1999OL667>.



Scheme 141

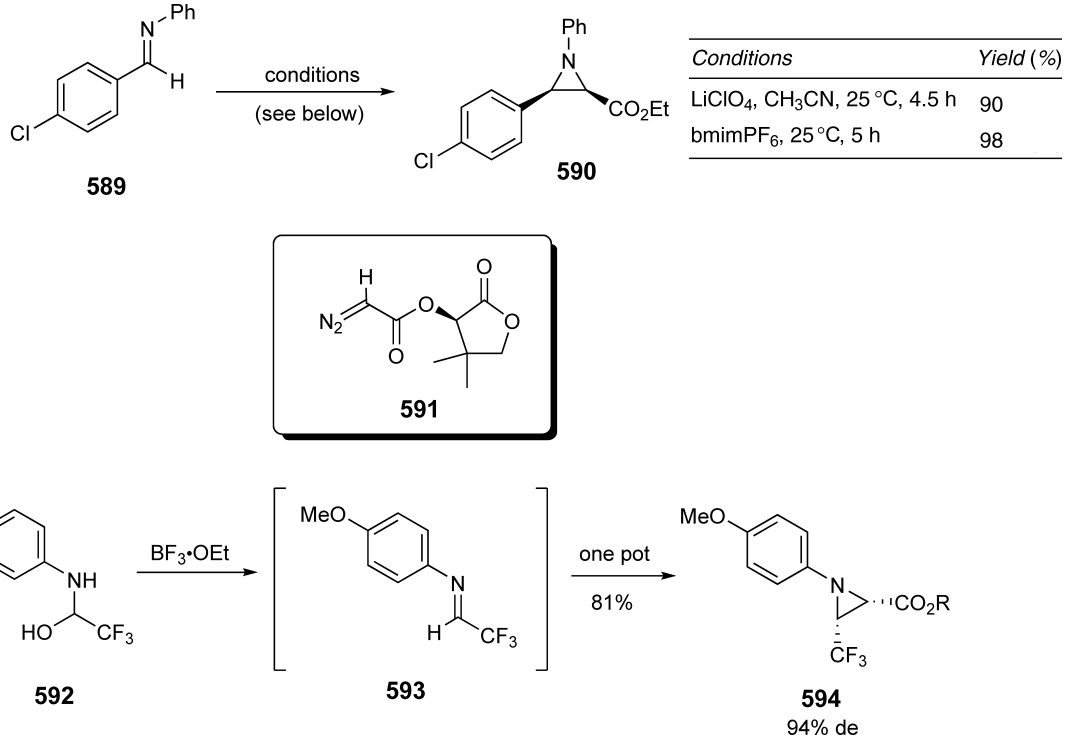
Trimethylsilyldiazomethane **585** smoothly reacts with *N*-sulfonylaldimines **582** to give 2-substituted *N*-sulfonyl-3-trimethylsilylaziridines **584** with high *cis*-selectivity <2000TL9455>. The reaction of ethyl diazoacetate can be catalyzed

by $InCl_3$ <2000TL6245> or by iridium complexes. In the latter case, the aldimines can be generated *in situ* in a one-pot, three-component procedure to give ethoxycarbonyl aziridines **588** in generally good yield (**Scheme 142**) <2000CC625>.



Scheme 142

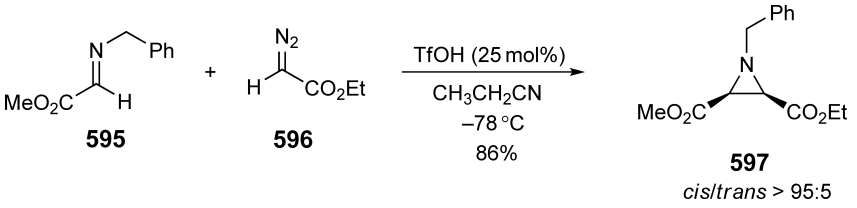
Ethyl diazoacetate is a frequently encountered carbene donor for the methylenation of imines. For example, the imine derived from *p*-chlorobenzaldehyde **589** is converted to the *cis*-aziridinyl ester **590** upon treatment with ethyl diazoacetate in the presence of lithium perchlorate <2003TL5275>. These conditions have also been applied to a reaction medium of the ionic liquid 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ($bmimPF_6$) with excellent results <2003TL2409>. An interesting enantioselective twist to this protocol has been reported, in which a diazoacetate derived from (*R*)-pantolactone **591** is used. This system was applied to the aziridination of trifluoromethyl-substituted aldimines **593**, which were prepared *in situ* from the corresponding aminals **592** under the catalysis of boron trifluoride etherate to give aziridines **594** (**Scheme 143**) <2003TL4011>.



Conditions	*Yield* (%)
$LiClO_4$, CH_3CN, 25 °C, 4.5 h	90
$bmimPF_6$, 25 °C, 5 h	98

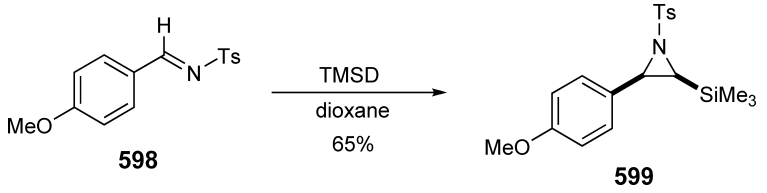
Scheme 143

Ethyl diazoacetate can also serve as an acetate enolate synthon under acidic conditions, engaging in [2+1] annulation with *N*-alkyl aldimines (e.g., **595**) to provide the corresponding aziridine (**597**) with very high *cis*-selectivity. The conditions are mild enough that acid-catalyzed ring opening of the products is not observed (**Scheme 144**) <2004JA1612>.



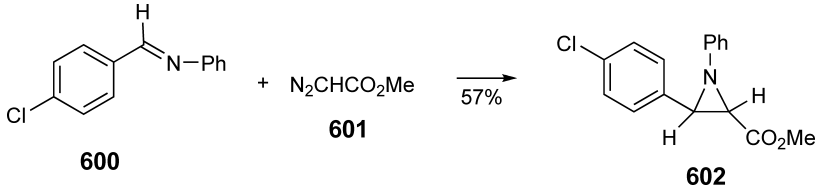
Scheme 144

Aggarwal *et al.* have reported a highly diastereoselective aziridination of imines with trimethylsilyldiazomethane (TMSD). Thus, tosylimine **598** was converted to the *cis*-aziridine **599** in 65% yield (**Scheme 145**) <2002JOC2335>.



Scheme 145

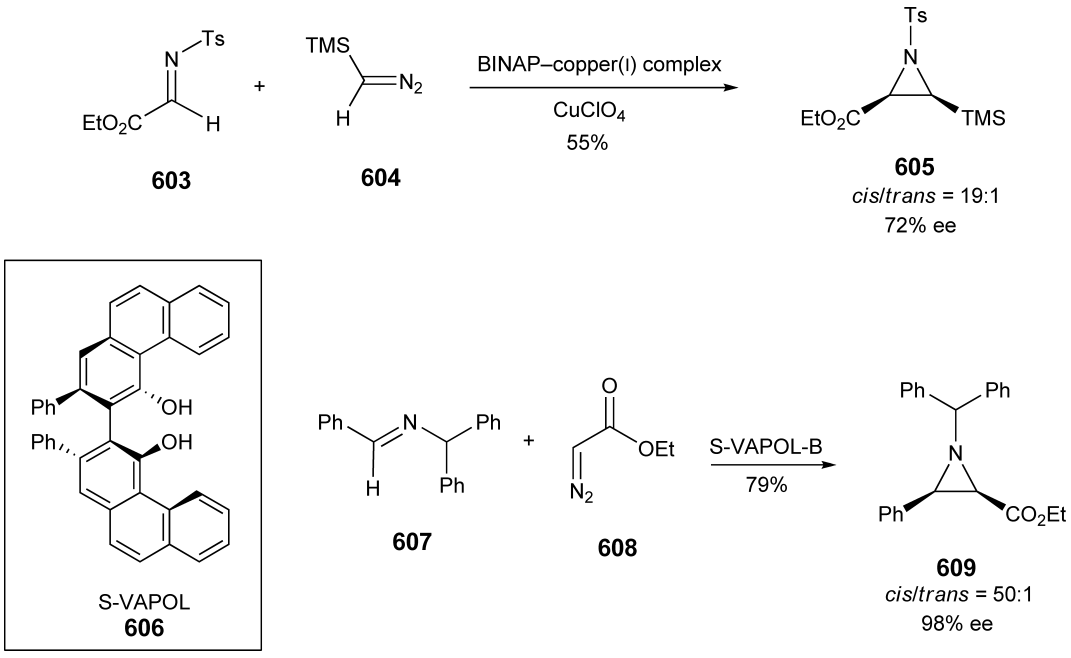
Two new heterogeneous catalysts have been prepared by exchanging a Montmorillonite K-10 clay with dilute solutions of $RhCl_3$ and $Mn(NO_3)_3$, respectively. These catalysts are effective for the synthesis of *trans*-aziridines (e.g., **602**) from imines (e.g., **600**) and methyl diazoacetate (**Scheme 146**) <1997CC1429>.



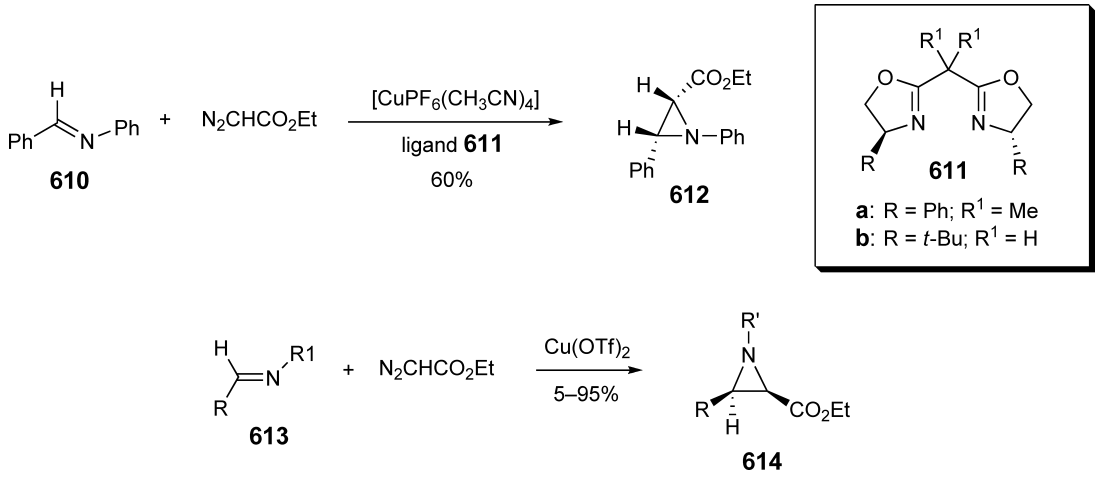
Scheme 146

As with epoxide synthesis, formation of optically pure aziridines is of ever-increasing interest. In this regard, the asymmetric aziridination of α-imino esters **603** can be promoted by copper(I) catalysts equipped with chiral BINAP or bis-oxazoline ligands. In this case, the asymmetric induction is believed to occur through a pre-coordination of the imino ester with the catalyst <1999J(P1)2293>. Simple imines, such as **607**, undergo aziridination under the influence of the chiral boron Lewis acid derived from S-VAPOL **606** to provide scalemic aziridines in excellent ee's in almost all cases (**Scheme 147**). Yields are fair to good <1999JA5099>.

The Jacobsen group has been active in the area of asymmetric synthesis of aziridines using the route of carbenoid transfer to imines and employing copper(I) salts in association with bis(dihydrooxazole) ligands **611** (**Scheme 148**), a process which yields modest ee's starting from imine **610** <1995AGE676>. Rasmussen and Jørgensen have also reported a similar racemic version of this protocol which features the copper(II) triflate-catalyzed group transfer from ethyl diazoacetate to various imines **613** to give the corresponding aziridines **614** as a mixture of *cis*- and *trans*-isomers; however, they report low ee's for the corresponding chiral approach using chiral ligand **611a** <1995CC1401>.



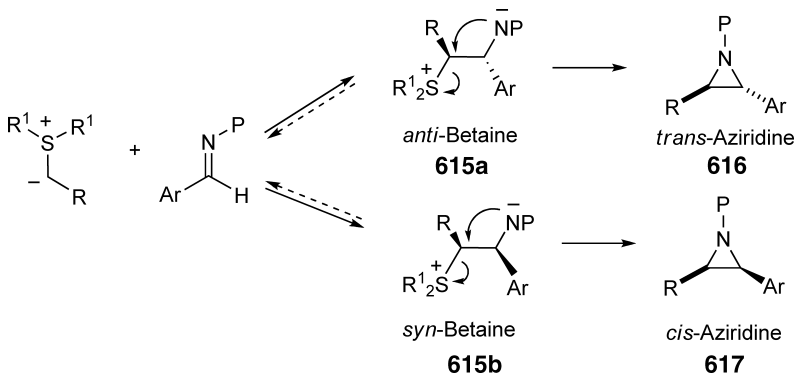
Scheme 147



Scheme 148

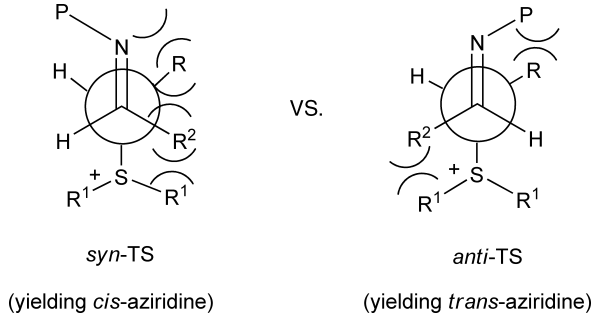
1.01.6.3.2 Preparation of aziridines using sulfur ylides and imines

Another variation of the [C+C=N] pathway involves the addition of sulfur ylides to imines and this method has been effectively used to access a wide range of substituted aziridines under mild reaction conditions. Although high ee's can be achieved by using a chiral sulfide (up to 98%), the *cis*/*trans*-diastereoselectivity in this process is, in most cases, poor. The generally accepted mechanism for aziridine formation from sulfur ylides and imines involves two key steps (**Scheme 149**) <2006JOC2726>. The first is addition of the ylide to the imine to form a betaine intermediate **615**. Two isomeric betaines (**615a** vs. **615b**) can be formed during this step: an *anti*- and a *syn*-diastereomer. The *transoid*-conformer (aza and sulfonium groups *anti*-periplanar to each other) of each of these betaines can then ring-close to yield a *trans*- **616** and a *cis*-aziridine **617**, respectively.



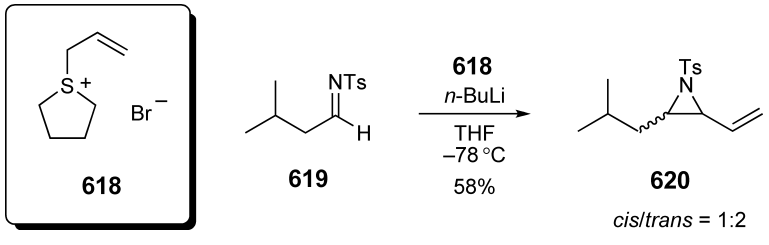
Scheme 149

Aggarwal *et al.* have suggested that the *anti*-betaine (leading to *trans*-aziridine) was formed preferentially in the reaction of *N*-sulfonylimines with semistabilized ylides (**Scheme 150**) <2001J(P1)3159>. This was attributed to steric strain in the transition state leading to the *syn*-betaine. In this model, ylides add to imines via transition states with a *transoid*-arrangement of the aza and sulfonium groups. Comparing the two diastereomeric transition states, *syn* and *anti*, it was suggested that the lesser steric encumbrance between the ylidic substituent (R) and the approaching imine in the *anti*-transition state accounts for the preferential formation of the *anti*-betaine and hence *trans*-aziridine with this system.



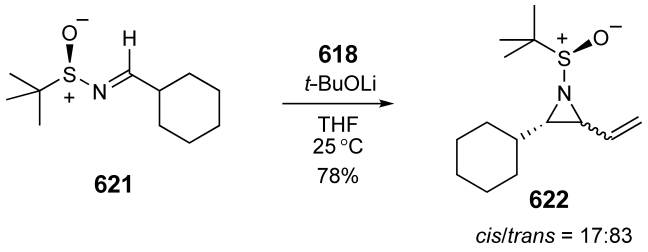
Scheme 150

In a typical example for aziridine synthesis, *S*-allyl tetrahydrothiophenium bromide **618** was smoothly deprotonated with strong base to provide an ylide which adds to a variety of N-protected imines. For the *N*-tosyl aldimine **619** derived from isovaleraldehyde, the corresponding vinyl aziridine **620** is formed in fair yield as a mixture of stereoisomers (**Scheme 151**) <2004TL1589>.



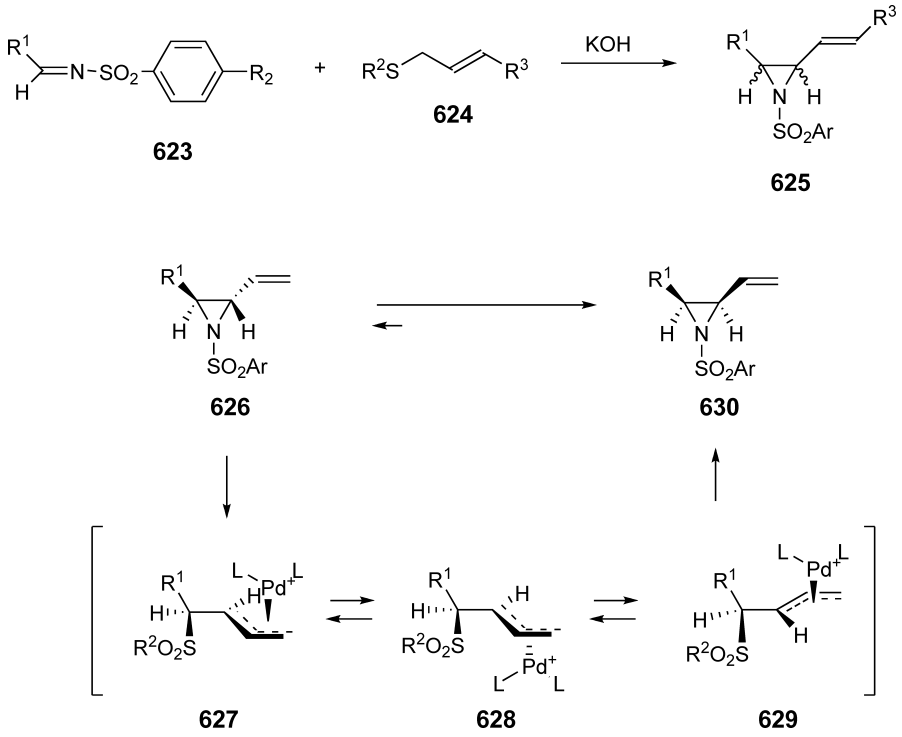
Scheme 151

When chiral *t*-butylsulfinylimine **621** is used as the substrate, a highly stereoselective aziridination ensues, providing the heterocycle **622** in good yield and good to excellent de (**Scheme 152**) <2004OL2377>.



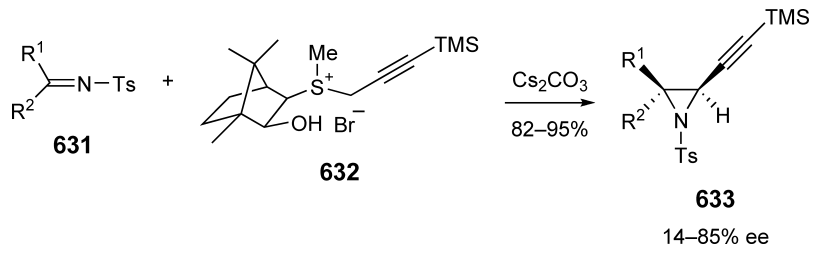
Scheme 152

Dai and co-workers <1996JOC4641, 1996CC491> have utilized the ylide–imine strategy in developing a direct route to *C*-vinylaziridines **625**. Thus, allylic sulfonium salts (i.e., **623**) react with aromatic, heteroaromatic, and α,β-unsaturated *N*-sulfonylimines (i.e., **624**) under solid–liquid phase-transfer conditions in the presence of KOH at room temperature to produce vinyl aziridines **625** (**Scheme 153**). Yields are excellent, but *cis*/*trans*-selectivity is modest. Interestingly, however, it has been demonstrated that the isomerization of such mixtures is feasible under palladium(0) catalysis. Under these conditions, *N*-arylsulfonyl-*trans*-3-alkyl-2-vinylaziridines are converted almost quantitatively to the corresponding *cis*-isomers through the intermediacy of a palladium–allyl complex. The observed apparent thermodynamic preference of the *cis*-isomer is in agreement with *ab initio* calculations <1996CC351>.



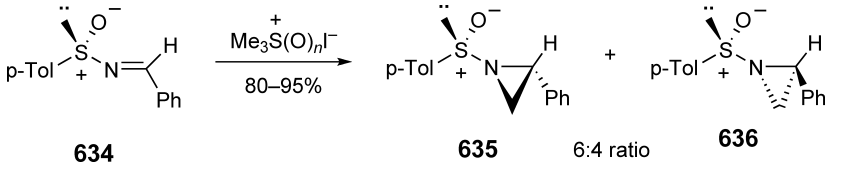
Scheme 153

The reaction of sulfur ylides with imines is an operationally straightforward procedure which is often carried out under phase-transfer conditions <1997TL7225>. The use of a chiral auxiliary allows the preparation of enantiomerically enriched aziridines, as illustrated by the reaction of *N*-sulfonylimine **631** with chiral sulfonium propargylide **632** to give the chiral aziridine **633** (**Scheme 154**) <1997AGE1317, 1998JOC4338>. *cis*-Selectivity is excellent, yields are good, and asymmetric induction, while generally modest, can also be quite high (up to 85%). The reader is directed to a recent review of the aziridination reaction via the ylide route <2006SL181>.



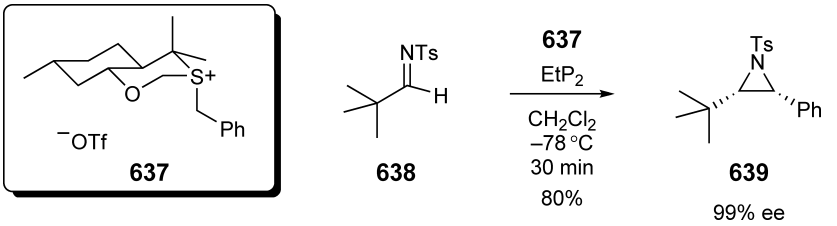
Scheme 154

The stereochemical outcome of the asymmetric aziridination route seems to be dependent upon the nature of the methylene-transfer reagent. Thus, dimethyloxosulfonium methylide provided predominantly isomer **635**, whereas the use of dimethylsulfonium methylide led to the formation of **636** as the major product (**Scheme 155**) <1995TL295>.



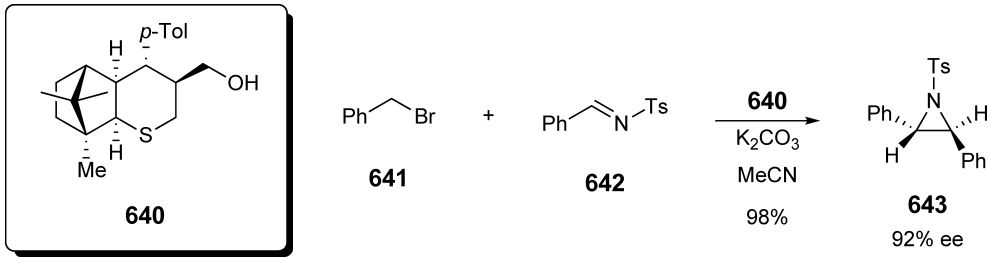
Scheme 155

Chiral induction can also be quite effective when the locus of asymmetry is attached to the sulfur ylide itself. The sulfonium salt **637**, derived from Eliel's oxathiane, can be used to deliver a benzylic center to tosylimines (e.g., **638**) and efficiently produces phenylaziridines with a very high degree of asymmetric induction. The method is amenable to gram-quantity synthesis, and the chiral auxiliary can be easily recovered. In general, *cis*/*trans*-mixtures are obtained, depending upon the steric bulk of the imine substituent (**Scheme 156**) <2004JOC1409>.



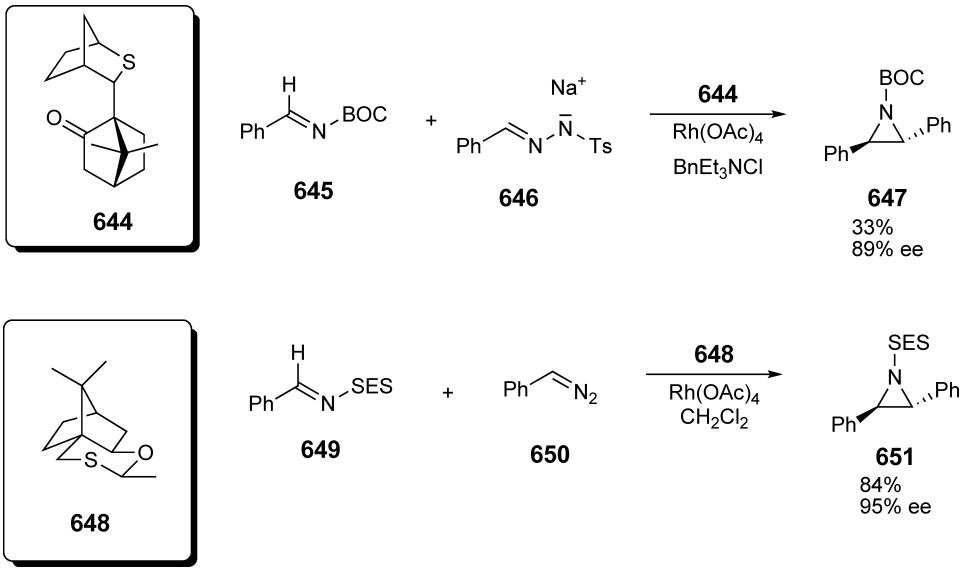
Scheme 156

Aziridines can also be synthesized enantioselectively from imines and alkyl halides using a camphor-derived chiral sulfide mediator **640** in a one-pot procedure via the imino Corey–Chaykovsky reaction. Thus, benzyl bromide **641** and tosyl imine **642** provide aziridine **643** in practically quantitative yield as a 3:1 mixture of (*E*/*Z*)-isomers and in 92% ee ((*E*)-isomer) (**Scheme 157**). An electron-withdrawing substituent on the imine nitrogen is necessary to activate the π-system for nucleophilic attack <2001TL5451>.



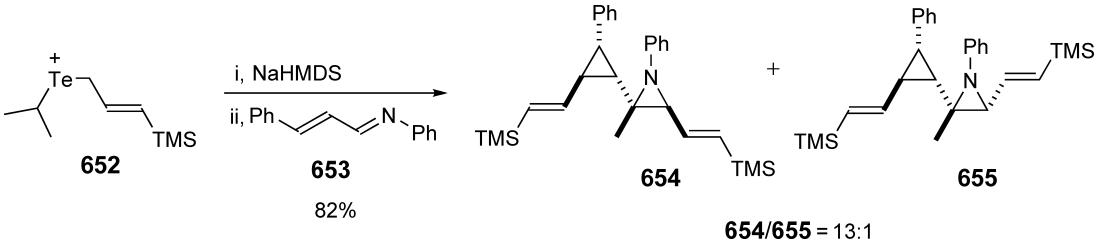
Scheme 157

Aggarwal *et al.* have applied their sulfur ylide methodology to the synthesis of aziridines with notable success. Thus, the ylides derived from chiral sulfide **644** and rhodium carbenoids (generated *in situ*) provide chiral aziridines (e.g., **647**) from imine precursors (e.g., **645**) (**Scheme 158**). The protecting group on the imine nitrogen plays a large role in yield and diastereomeric ratios, and to a lesser extent on the enantioselectivity. The BOC group gives the best *trans*/*cis*-ratio, but the lowest overall yield. The opposite is true for the SES group. Enantiomeric excesses range from 89% to 98% <2001AGE1433>. The SES group also turns out to be the best choice when the sulfide **648** is used as the chiral auxiliary. Solvent and substrate structure also influence the selectivity <2001J(P1)1635>.



Scheme 158

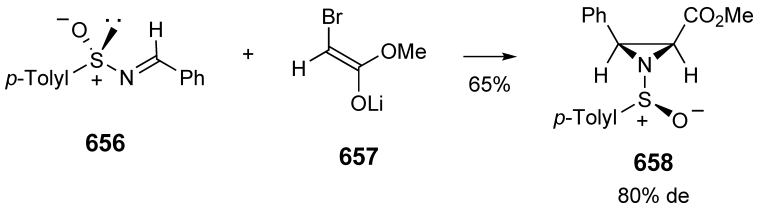
The related telluronium ylides also add to α,β-unsaturated imines through a Michael addition–elimination to the olefin followed by a second equivalent of telluronium ylide addition to the imine, which subsequently eliminates to form aziridines **654** and **655** in a ratio of 13:1 (**Scheme 159**) <2005JA12222>.



Scheme 159

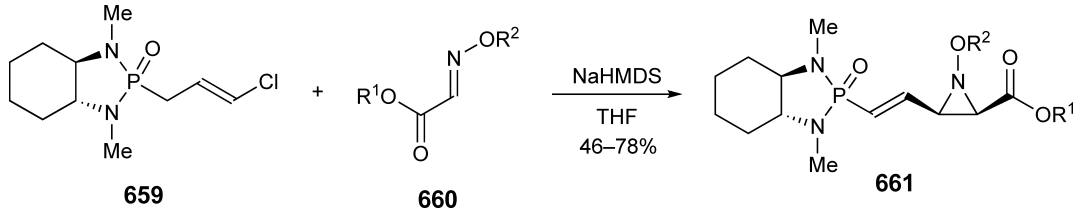
1.01.6.4 Anion Addition–Elimination Approach

The Gabriel–Cromwell approach proceeds through the intramolecular displacement of the halide in the cyclization step, and this end game can be approached from more than one starting point. Thus, Davis *et al.* <1999JOC7559> reported on a one-step aza-Darzens reaction of sulfinimines **656** with lithium α-bromoenolates **657** to give the corresponding aziridines **658** in fair to good yield and good to excellent de (**Scheme 160**). The *cis*/*trans*-isomer ratio is dependent upon the nature of the bromoenolate, with the anion of α-bromoacetate itself giving rise to predominantly the *cis*-isomer **658**, and substituted analogs producing mainly the *trans*-isomer. This selectivity was rationalized on the basis of a chair-like transition state.



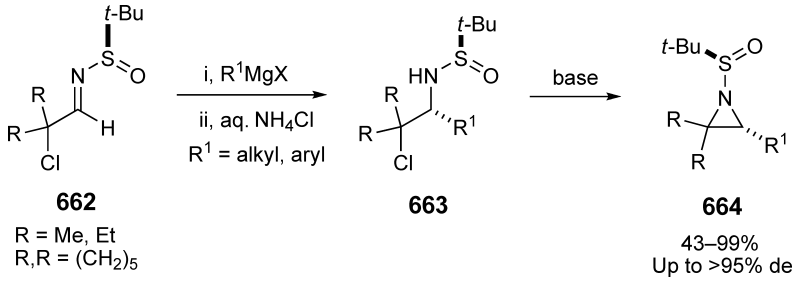
Scheme 160

In an anionic approach, the sodium salt of the chiral chloroallyl phosphonamide **659** engages in nucleophilic addition onto oximes and gives the optically pure *N*-alkoxy aziridines **661** (**Scheme 161**). The chiral auxiliary can be removed by oxidative cleavage of the double bond with ozone <2000TL787>.



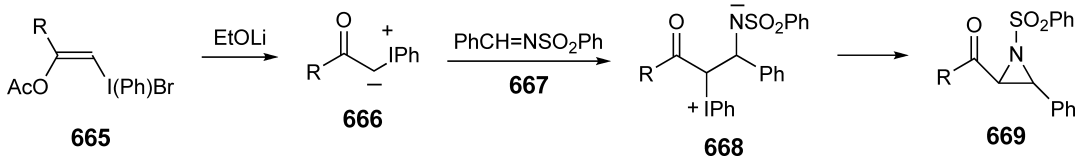
Scheme 161

Reaction of chiral α-chloro *tert*-butanesulfinyl aldimines **662** with Grignard reagents efficiently affords β-chloro-*N*-sulfinamides **663** with high de. These compounds were cyclized to give the corresponding chiral aziridines **664** in a high-yielding one-pot reaction or after separate treatment with base. The diastereoselectivity obtained in the newly synthesized β-chloro sulfinamides was explained via the coordinating ability of the α-chloro atom with magnesium which results in the opposite stereochemical outcome as generally observed for nonfunctionalized *N*-sulfinylimines (**Scheme 162**) <2006OL3129>.



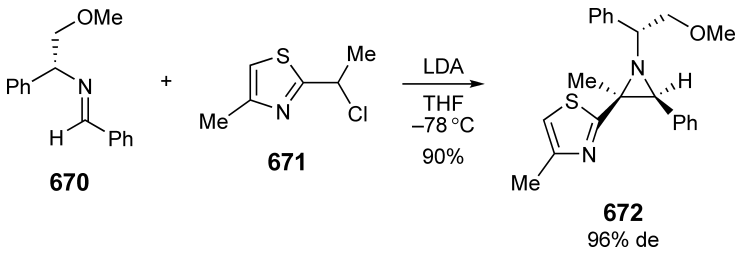
Scheme 162

Monocarbonyl iodonium ylides such as **666** have been generated *in situ* from iodoenol ester precursors **665**. These reagents undergo alkylidene-transfer reactions with activated imines (e.g., **667**) to give α,β-aziridino ketones, mainly as the *cis*-isomer. The selectivity of the aziridination was noted to be slightly increased by the presence of electron-donating substituents on the imine *C*-phenyl ring (**Scheme 163**) <1998TL5569>.



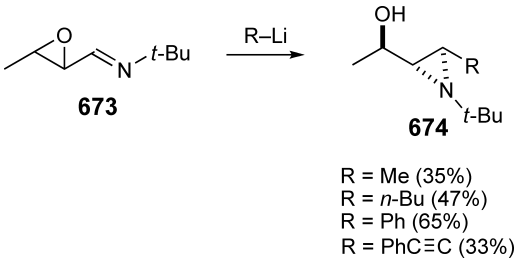
Scheme 163

The approach of leveraging chirality at the imine nitrogen to impart enantioselectivity has also been used to advantage in the preparation of chiral heterosubstituted aziridines. Thus, when 2-(1-chloroethyl)-4-methyl-thiazole **671** is deprotonated with lithium diisopropylamide (LDA) and treated with the chiral aldimine **670**, the aziridinyl thiazole derivative **672** is produced in excellent yield and diastereoselectivity (**Scheme 164**) <2004T1175>.



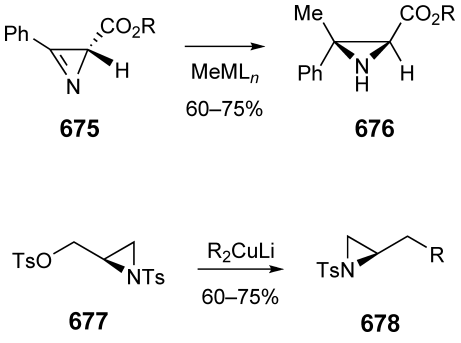
Scheme 164

A new example of the aza-Payne rearrangement has been used to prepare α-hydroxyaziridines <2005OL3267>. The epoxy imine **673** is prepared by a sequential epoxidation and imination. Reaction of **673** with a series of alkyllithium reagents initially adds to the imine which then does an aza-Payne rearrangement to form the hydroxyaziridine **674** (**Scheme 165**). While the method generally suffers from poor yields, the one-step nature of the transformation lends greatly to its appeal.



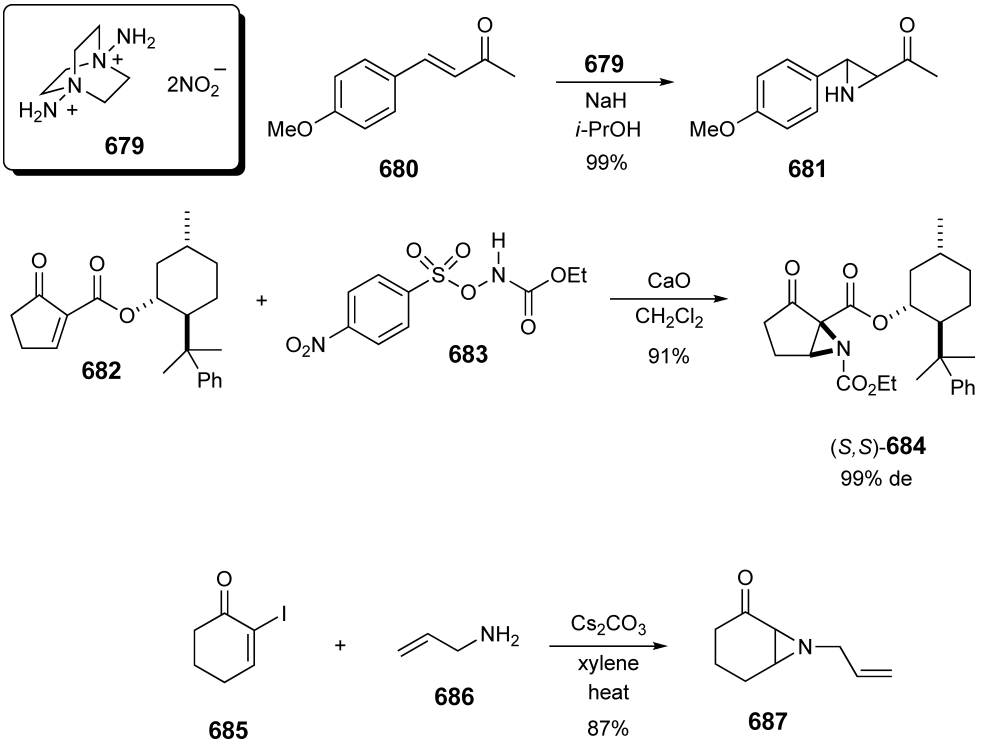
Scheme 165

The addition of Grignard reagents onto chiral azirenes (e.g., **675**) has been used for the highly stereoselective preparation of unsymmetrical 3,3-disubstituted-aziridine-2-carboxylate esters (e.g., **676**), themselves useful precursors for the synthesis of unnatural β-substituted α-amino acids <1997JOC3796>. Organometallic reagents can also engage in nucleophilic attack on the aziridine nucleus, which Bergmeier and Seth <1997JOC2671> use to advantage in their synthesis of monosubstituted alkyl aziridines **678** starting from the chiral tosylated derivative **677**, a reaction which occurs without the loss of optical purity (**Scheme 166**).



Scheme 166

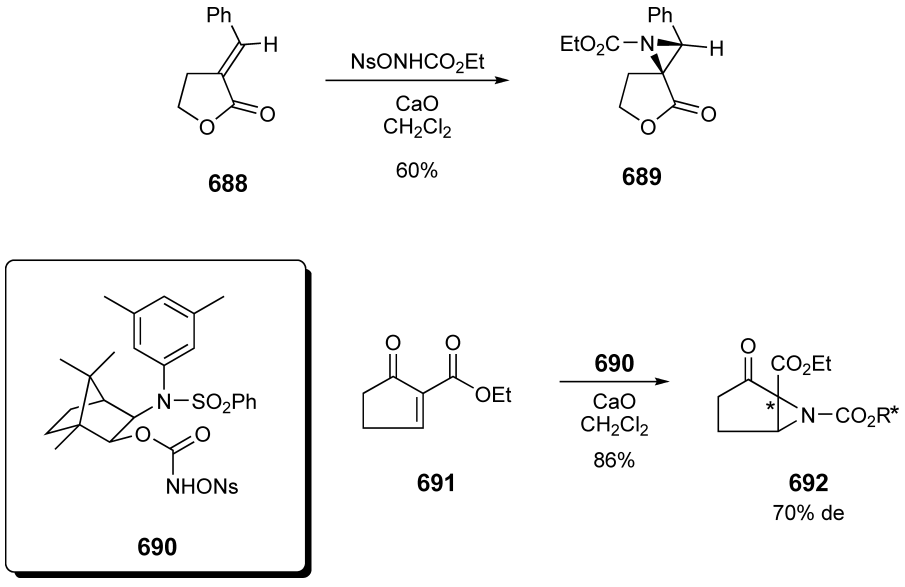
Electron-deficient alkenes can be converted to aziridines using nucleophilic nitrogen donors attached to good leaving groups. For example, *N,N′*-diazoniabicyclo[2.2.2]octane dinitrate **679** forms a nitrogen–nitrogen ylide in the presence of sodium hydride, which converts enones directly to the unprotected aziridines (e.g., **681**) by way of initial Michael addition and subsequent cyclization <2002J(P1)1491>. Another method employs the anion of nosyloxycarbamate **683** as the aziridinating agent and a diactivated substrate which is equipped with a phenylmenthol chiral auxiliary appended to the ester moiety. Thus, enone ester **682** is converted to the azabicyclo[3.1.0]hexanone derivative **684** in 91% yield and 99% de upon treatment with **683** and calcium oxide <2002JOC4972>. In the case of α-iodoenones (e.g., **685**), even simple primary amines can engage in aziridination, a process which is mediated by cesium carbonate (**Scheme 167**) <2002TL4329>.



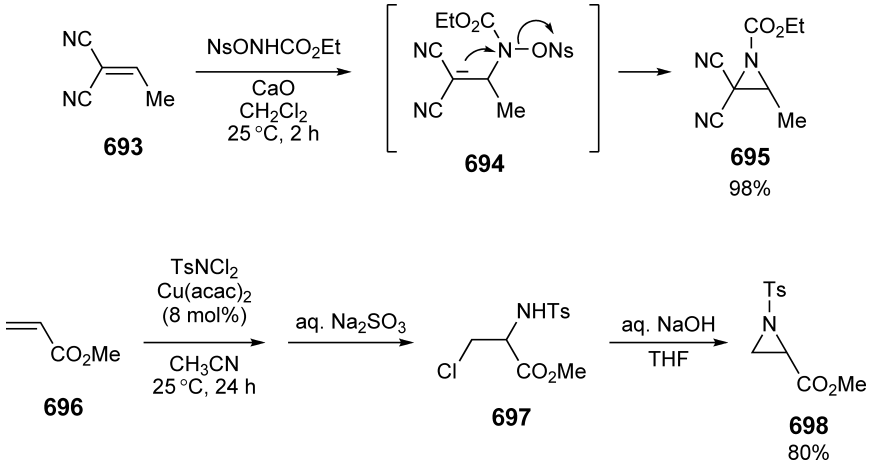
Scheme 167

Exocyclic α,β-unsaturated lactones (e.g., **688**) have been converted to the corresponding spiroaziridines **689** by treatment with ethyl *N*-{[(4-nitrobenzene)sulfonyl]oxy}carbamate ($NsONHCO_2Et$) in the presence of calcium oxide <2003TL4953>. In a similar vein, a novel chiral carbamate **690** based on Helmchen's alcohol has been applied to the same conditions with moderately good diastereoselectivities, as shown in the aziridination of carboethoxy-cyclopentenenone **691** (**Scheme 168**) <2003TL3031>.

In the case of electron-deficient olefins, other methodologies are also available. For example, the dicyanoalkene **693** (derived from the Knoevenagel condensation of malononitrile with acetaldehyde) undergoes a facile aza-Michael addition of ethyl nosyloxycarbamate in the presence of calcium oxide to give a β-aminocarbanion intermediate **131**, which quickly cyclizes to the corresponding dicyanoaziridine **695** in excellent yield <2004SL1083>. When trifluoromethylacrylates are used as substrates, the intermediate Michael adducts can be isolated in >95% yield <2004OL197>. Some degree of enantioselectivity has been observed when *Cinchona* alkaloids are used as catalysts in the reaction <2004T8073>. An electrophilic variant is represented by the copper-catalyzed addition of *N,N*-dichloroarylsulfonamide across electron-deficient olefins such as methyl acrylate **696**. The resulting β-chloroamines, which exhibit stereochemistry resulting from net *anti*-addition, can be cyclized by treatment with sodium hydroxide to provide tosyl aziridines (e.g., **698**) in good overall yield (**Scheme 169**) <2004SC1337>.



Scheme 168



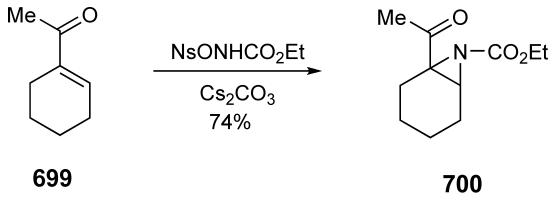
Scheme 169

Pellacani and co-workers have reported on the aziridination of α,β-unsaturated ketones (e.g., **699**) <1998T14105> and α-nitroalkenes (e.g., **701**) <1998T6169> using a system of ethyl [(4-nitrobenzenesulfonyl)oxy]carbamate ($NsONHCO_2Et$) as the nitrene donor and calcium oxide as the base (**Scheme 170**). The reaction can be carried out in the absence of auxiliary solvent and is suspected to proceed via an aza-Michael route, rather than by a true nitrene-addition pathway.

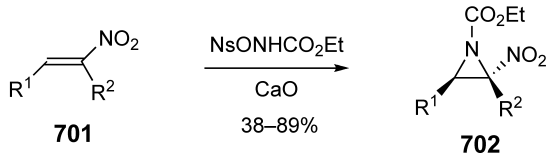
Aziridination of electron-deficient olefins usually proceeds by a conjugate addition pathway. Thus, benzylamine adds to 2-(5*H*)-furanon-3-yl methanesulfonate **703** to give a Michael adduct **704**, which ring-closes to form the corresponding aziridine **705** <2000TL3061, 2000TL6393>. Ring-closure strategies have also been used in other systems not constructed directly from electron-deficient olefins. For example, the chloroamino ester **708**, derived from the action of alanine dehydrogenase on keto acid **706**, undergoes base-catalyzed ring closure to form an aziridine <2000CC245>, as does the β-alkylamino phenylselenide **710**, which is prepared from an α-phenylselanyl imine (**Scheme 171**) <2000TL663>.

Similarly, chiral aziridinoalcohols **714** are readily obtained from the reaction of racemic methyl 2,3-dibromopropionate **712** and optically pure 2-phenylglycinol **713** (**Scheme 172**) <2000SC1303>.

Alkenes undergo diastereoselective aziridination in the presence of chiral 3-acetoxyaminoquinazolinones (e.g., **715**), prepared *in situ* by acetoxylation of the corresponding 3-aminoquinazolinones. Thus, trimethylsilyl styrene **716**

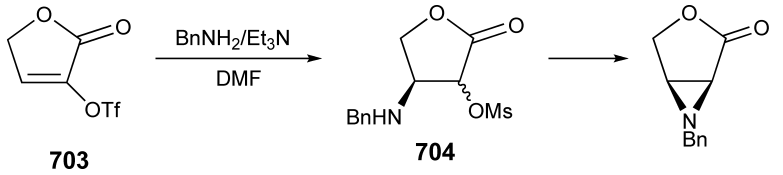


699 700

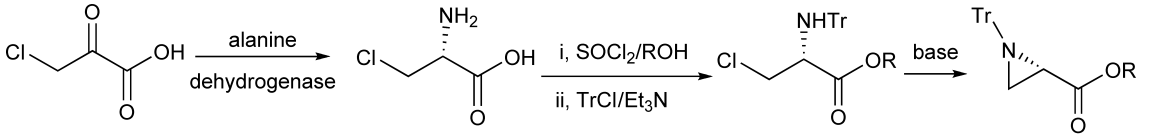


701 702

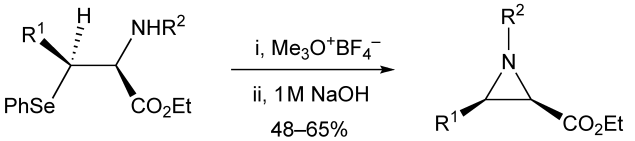
Scheme 170



703 704 705
55%

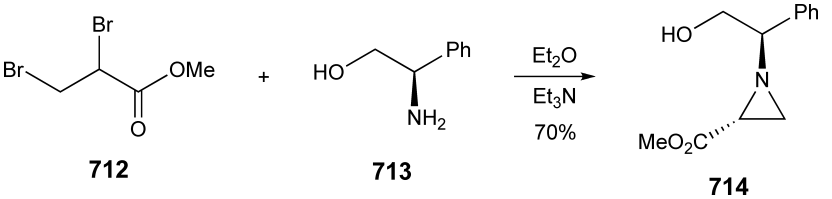


706 707 708 709
90–98%



710 711

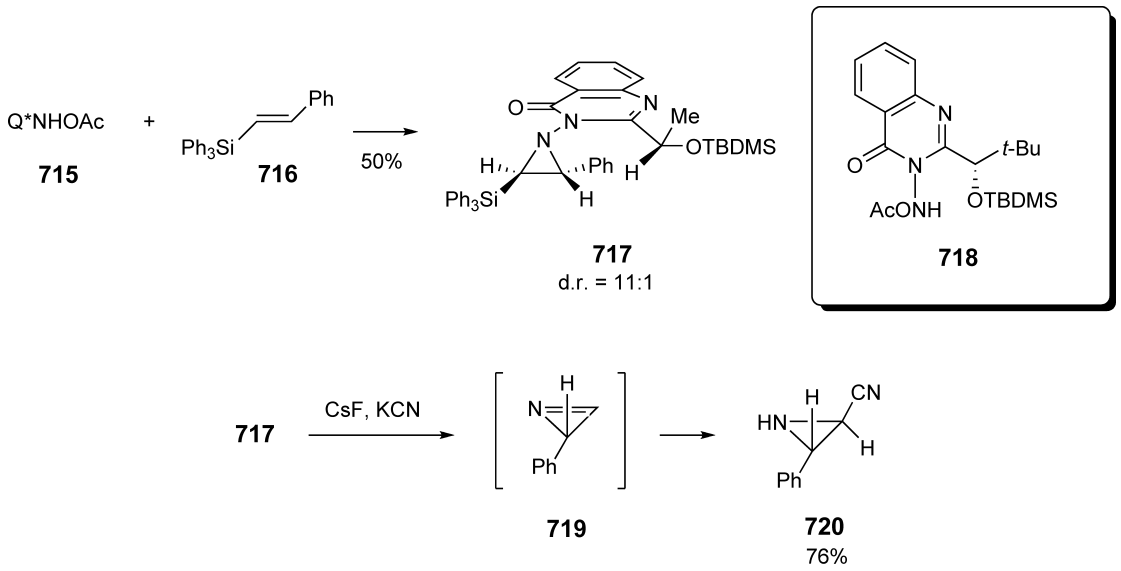
Scheme 171



712 713 714

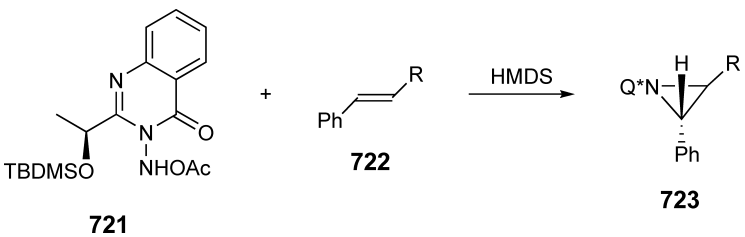
Scheme 172

is converted to the aziridine **717** with a diastereomeric ratio of 11:1. The diastereoselectivity is rationalized by a transition state which maximizes *endo*-overlap of the substrate phenyl ring with the reagent π-system, while minimizing nonbonded interactions, a factor largely dominated by the relative steric volumes of the two substituents on the chiral carbon center. This is illustrated by a sharp drop in the diastereoselectivity of this reaction (4:1) when the bulkier *t*-butyl group is substituted for the methyl group (i.e., **718**) <1996TL5179>. After aziridination, the chiral auxiliary can be removed by desilylative elimination to give an intermediate azirine **719**, which can be trapped *in situ* by the addition of cyanide, providing the NH-aziridine **720** with 83% ee (**Scheme 173**) <1996CC789>.



Scheme 173

3-Acetoxyaminoquinazolinones **721** have been found to function as chiral aziridinating agents for alkenes. Aziridine formation proceeds with retention of alkene configuration via a mechanism analogous to the epoxidation of alkenes with peroxyacetic acid (**Scheme 174**). In the case of styrene derivatives (e.g., **722**), diastereoselectivity increases as the *β*-substituent (R) becomes more electronegative, with an observed diastereomeric ratio of 5:1 for the methyl derivative and 20:1 for the dichloromethyl analog. These results were rationalized on the basis of a tighter and more symmetrical transition state, as predicted by highest occupied molecular orbital–lowest unoccupied molecular orbital (HOMO–LUMO) considerations <1998TL5113, 1998J(P1)583>.

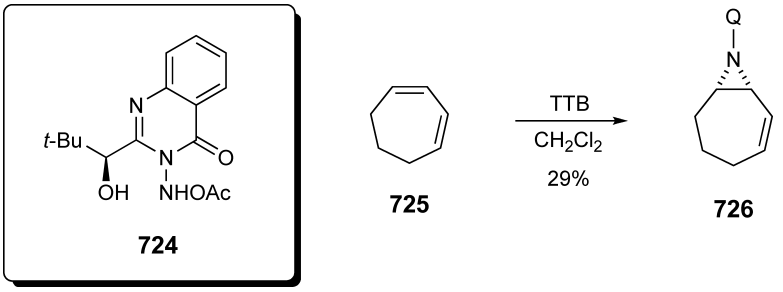


Scheme 174

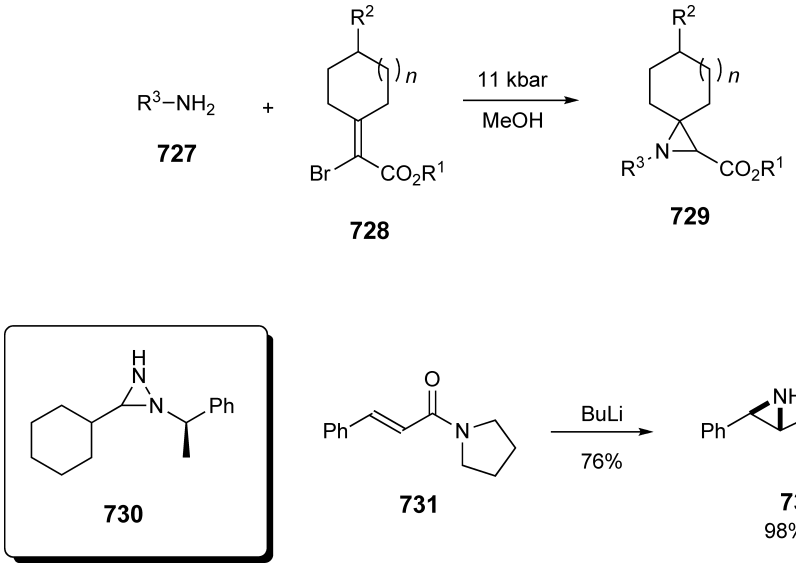
Other approaches to chiral aziridines have been reported. For example, treatment of cycloheptadiene **725** with the leucine-derived (*S*)-3-acetoxyamino-2-(3-hydroxy-2,2-dimethylpropyl)quinazolin-4(3*H*)-one **724** in the presence of titanium(IV) *t*-butoxide (TTB) in methylene chloride leads to formation of the chiral aziridine **726**, in which the chiral auxiliary (Q) is in the *exo*-position, as the only isolated product in 29% yield (**Scheme 175**) <2001J(P1)1518>.

The aziridination of electron-deficient alkenes can be carried out under slightly different conditions. The reaction between primary amines **727** and 2-bromo-2-(cycloalkylidene)acetates **728** in alcohol under high pressure provides spiroaziridines **729** in good yields and de's. The reaction is general for most primary amines, except for

those that are weakly nucleophilic or sterically bulky <2001EJO2569>. Enamides (e.g., **731**) can be converted to corresponding aziridinylamides **732** with excellent enantioselectivity using the chiral diaziridine **730** (**Scheme 176**) <2001CL984>.



Scheme 175

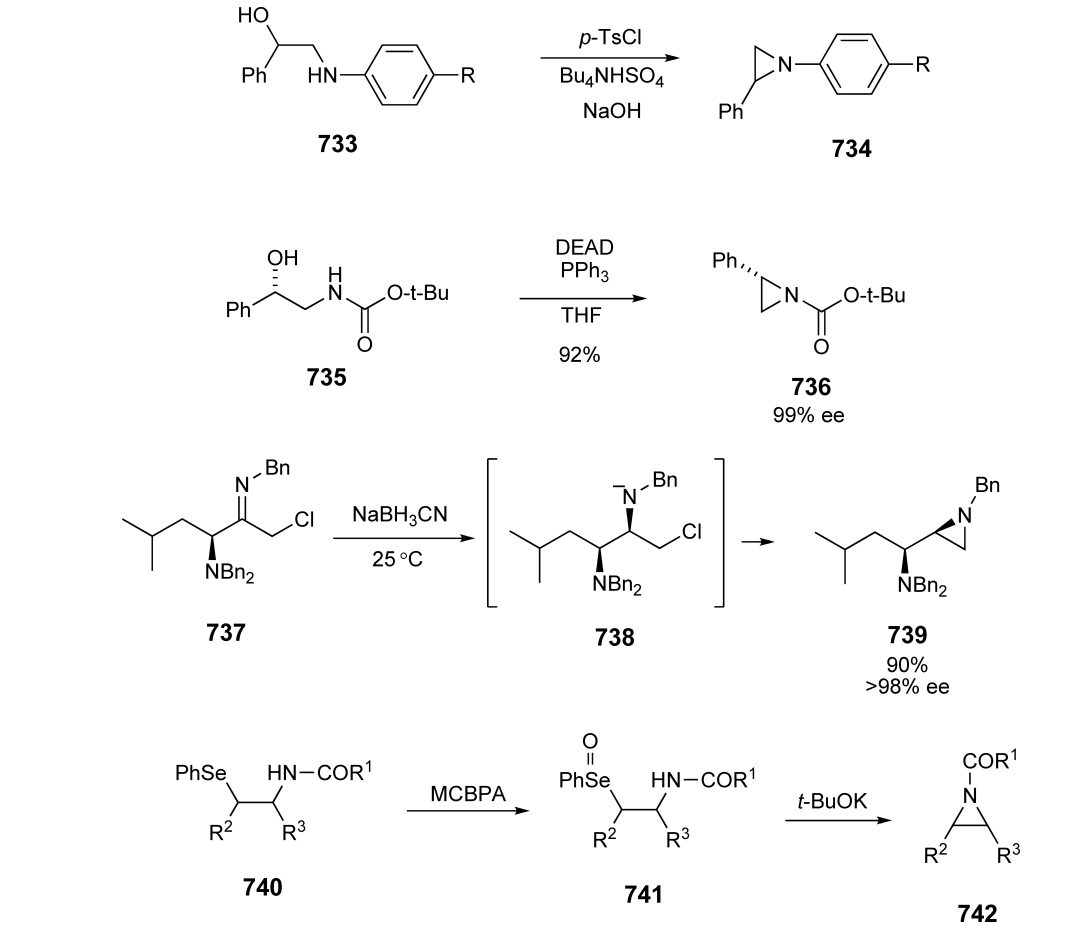


Scheme 176

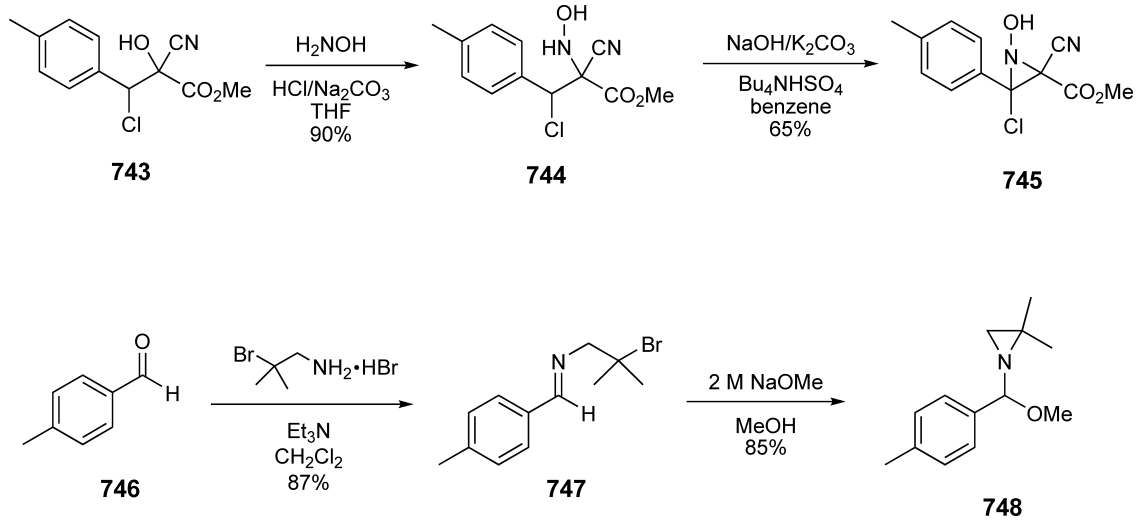
1.01.6.5 Cyclization of 1,2-Diamino Alcohols and Derivatives

Aziridines can also be formed by the ring closure of appropriately substituted amines. For example, treatment of *N*-aryl-*β*-amino alcohols **733** with *p*-toluenesulfonyl chloride under phase-transfer conditions provides *N*-aryl aziridines **734** in 80–90% yield <2001SC1105>. Enantiomerically pure aziridines can be prepared in a similar fashion, starting with optically pure amino alcohols derived from the enantioselective reduction of *α*-amino ketones. Thus, treatment of the amino alcohol **735** with diethyl azodicarboxylate (DEAD) and Ph_3P in THF led to the formation of aziridine **736** in 92% yield and 99% ee <2001J(P1)1916>. The chiral chloroimine **737** could be converted to the optically pure aziridine **739** via diastereoselective reduction with sodium cyanoborohydride to produce the intermediate amide anion, which cyclizes to form **739** in 90% yield and >98% ee <2001JOC2764>. Finally, the oxidation of *β*-amido selenides **740** with *m*-chloroperbenzoic acid (MCPBA), followed by treatment of the corresponding selenones with potassium *t*-butoxide, gives *N*-acylaziridines in good to excellent yields (**Scheme 177**) <2001J(P1)944>.

Of course, aziridines can also be synthesized by the ring-closing reactions of appropriately substituted amines. For example, halohydrins of type **743** are converted to *N*-hydroxy aziridines **745** by treatment with hydroxylamine derivatives, followed by base-catalyzed intramolecular S_N2 reaction of the intermediate *β*-haloaminoesters **744** under phase-transfer conditions <2003TL3259>. *N*-Bromoethylimines **747**, formed from the reaction of benzaldehyde derivatives (e.g., **746**) and 2-bromo-2-methylpropylamine hydrobromide, undergo nucleophilic attack by methoxide, followed by intramolecular displacement of bromide to form *N*-(*α*-methoxybenzyl)aziridines **748** (**Scheme 178**) <2003TL1137>.

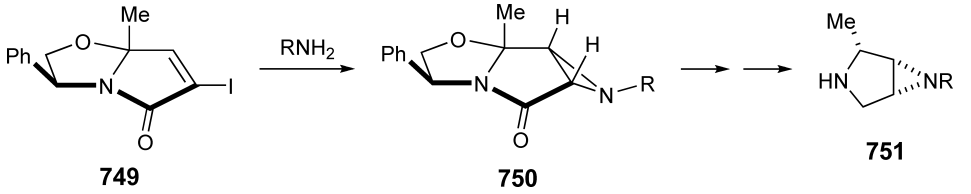


Scheme 177



Scheme 178

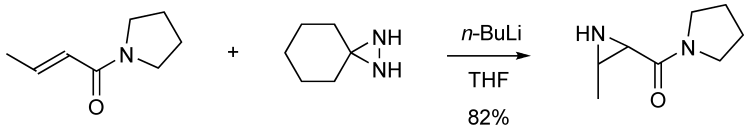
A strictly nucleophilic approach can also be used for an [N+C═C] protocol. Thus, the chiral iodo-unsaturated bicyclic lactam **749** undergoes stereoselective conjugate addition with primary amines to give the tricyclic aziridine **750**, which can be subsequently transformed into the chiral 3,4-aziridinopyrrolidine **751** by reductive cleavage. Yields of up to 90% can be achieved and facial selectivity is greater than 98:2 (**Scheme 179**) <1995TL3491>.



749 **750** **751**

Scheme 179

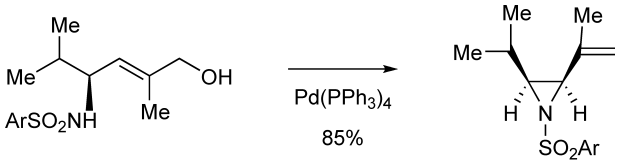
An interesting anionic aziridination of α,β-unsaturated amides was reported <1999TL5207>, utilizing lithiated 3,3-pentamethylenediaziridine **753** as the nitrogen atom donor (**Scheme 180**). Formation of *cis*-aziridines was generally observed, regardless of the stereochemistry of the starting material, a phenomenon which is in keeping with a stepwise mechanism of conjugate addition and subsequent ring closure.



752 **753** **754**

Scheme 180

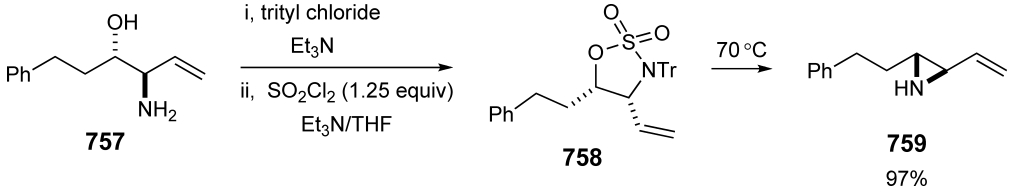
Sterically congested *cis*-aziridines such as **756** were prepared from the derivatized amino allyl alcohol precursor **755** through a palladium-catalyzed cyclization reaction <1999TL1331>. This methodology has also been extended to the cyclization of amino allenes (**Scheme 181**) <1999JOC2992>.



755 **756**
d.r. = 98:2

Scheme 181

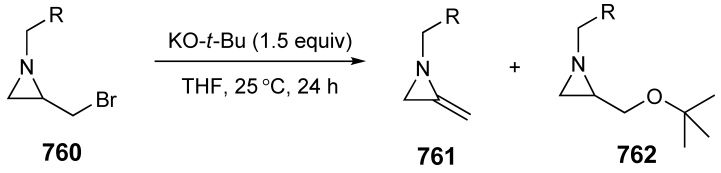
One straightforward route to the aziridine ring system is available through the ring closure of vicinal amino alcohols, an approach which has been used to prepare vinyl NH-aziridines. Thus, 4-amino-1-phenylhex-5-en-3-ol **757** was treated with sulfuryl chloride to provide the sulfamidate **758**, which underwent clean thermolysis at 70 °C to form the vinyl aziridine **759** in 97% overall yield (**Scheme 182**) <2002T5979>.



757 **758** **759**
97%

Scheme 182

Finally, some rather interesting but esoteric methyleneaziridines (e.g., **761**) have been prepared via the 1,2-dehydrobromination of 2-(bromomethyl)aziridines **760** under carefully controlled conditions (**Scheme 183**) <1997JOC2448>.



760 **761** **762**

Scheme 183

1.01.7 Introduction – Monocyclic 2*H*-Azirines

2*H*-Azirines correspond to the smallest nitrogen unsaturated heterocyclic system, with two carbon atoms and one double bond in a three-membered ring. The theoretical and biological applications and the synthetic chemistry of these heterocycles have been extensively explored and a number of general reviews on 2*H*-azirines have appeared <1996CHEC-II(1A)1, 2001EJO2401, 2002OPP219>. Substituted 2*H*-azirines are versatile compounds and have been used for the preparation of functionalized aziridines. The chemistry of 2*H*-azirines is dominated by processes in which the strain of the three-ring system is relieved. They readily participate in cycloaddition reactions as 2π-components and undergo ring cleavage on photochemical excitation to give nitrile ylides. These dipoles then undergo a subsequent 1,3-dipolar cycloaddition reaction with a variety of π-bonds. Thermal ring cleavage produces vinyl nitrenes by cleavage of the N–C_2 bond, which then undergo ring-expansion reactions.

1.01.8 2*H*-Azirines

1.01.8.1 Theoretical Methods

A number of the theoretical issues dealing with 2*H*-azirines were discussed in CHEC-II(1996) and CHEC(1984) <1996CHEC-II(1A)1, 1984CHEC(7)47>.

1.01.8.2 Experimental Structural Methods

The structures of 2*H*-azirines, their complexes with H^+ and Li^+, and the relative basicities of 2*H*-azirines have been calculated by semi-empirical and *ab initio* methods <1993JA11074, 1999PCA3330, 1998PCA7074>. The spectroscopic properties of 2*H*-azirines were discussed in detail in CHEC-II(1996) <1996CHEC-II(1A)1>. Polarization toward the more electronegative nitrogen atom of the 2*H*-azirine ring results in a shorter C–N bond and a longer C–C bond, consistent with the dimensions of 2*H*-azirines found by single crystal X-ray data <1997CEJ1757>.

1.01.8.3 Thermodynamic Aspects

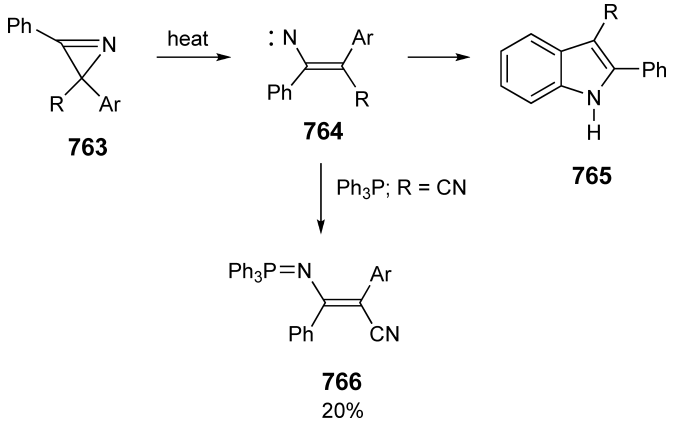
The stability of the 2*H*-azirine ring can be attributed not only to the combined effects of bond shortening and angle compression, but also to the presence of the electron-rich nitrogen atom. The strain energy associated with these heterocycles is principally due to deformation of the normal bond angles between the atoms of the ring. The total ring-strain energy of 2*H*-azirine has been estimated at 48 kcal mol^{-1} <1991AGE238, 2002EJO1750>, although lower values of 44.6 and 46.7 kcal mol^{-1} have been reported using *ab initio* calculations at the MP2/6-31G* and B3LYP/6-31G* levels of theory <1998JCC912>.

1.01.9 Reactivity of Monocyclic 2*H*-Azirines

The chemical reactivity of 2*H*-azirines is quite high as a consequence of their ring strain, reactive π-bond, and ability to undergo regioselective ring cleavage. 2*H*-Azirines not only are capable of acting as nucleophiles and electrophiles in organic reactions, but also can act as dienophiles and dipolarophiles in cycloaddition reactions. Consequently, they are useful precursors for the synthesis of a variety of nitrogen-containing heterocyclic systems.

1.01.9.1 Thermal Reactions of 2*H*-Azirines

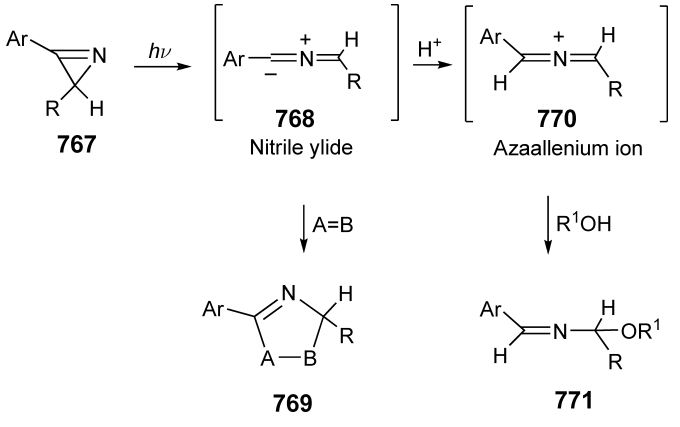
The major thermal reaction of 2*H*-azirines involves C(2)–N bond cleavage to form vinyl nitrene intermediates <1984CHEC(7)47, 1996CHEC-II(1A)1, 1998H(48)2551>. In a typical example, the thermolysis of aryl-substituted 2*H*-azirines **763** results in the formation of indoles **765** by intramolecular electrocyclization of the intermediate vinyl nitrene **764** with the aromatic ring <1996CHEC-II(1A)1>. In the case where a cyano group is present in the 2-position of the azirine ring, the vinyl nitrene intermediate can be trapped with triphenyl phosphine to give the conjugated phosphazene **766** (**Scheme 184**) <1999JOC6239, 1996T4857>.



Scheme 184

1.01.9.2 Photochemical Reactions of 2*H*-Azirines

2*H*-Azirines are photochemically highly active substances. Upon irradiation into their n–π^*-absorption bonds, the strained three-membered azirine ring **767** opens selectively at the C–C bond in a heterocyclic fashion leading to the formation of a nitrile ylide intermediate (i.e., **768**) <1973JA1954>. The nitrile ylide can be trapped by reactive dipolarophiles (A═B) to give five-membered rings **769**. A recent example of the 1,3-dipolar cycloaddition is the facile synthesis of exohedrally functionalized fullerenes <1996T5407>. In alcohols as solvents, the nitrile ylides are protonated to yield azallenium cations **770** which are then trapped by the alcohol to furnish alkoxyimines **771**. The protonation rate of the ylide in alcohol increases with the acidity of the alcohol. On the basis of a large kinetic isotope effect ($K_H/K_D = 5.5$) for protonation of the ylide, the transition state for the nitrile ylide protonation was concluded to be linear <1997JA11605> Ring expansion of the 2*H*-azirine to pentagonal heterocycles by photochemical isomerization was also reported to occur (**Scheme 185**) <1995HCA935>.

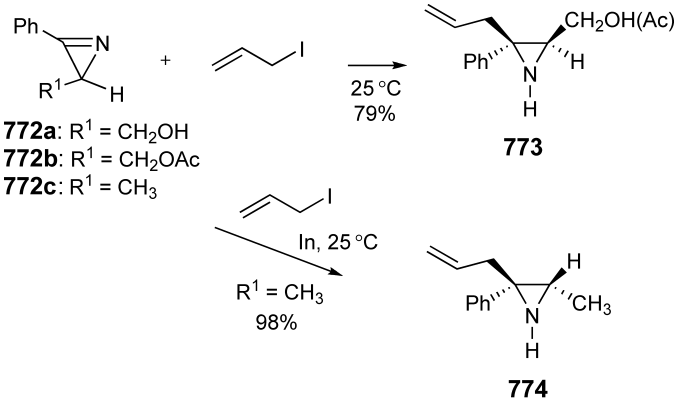


Scheme 185

More recently, the photochemistry of 3-methyl-2-(1-naphthyl)-2*H*-azirine has been investigated by the direct observation of reactive intermediates in Ar-matrices and by the characterization of reaction products in solution <2005JA2628>. Interestingly, the irradiation of this particular 2*H*-azirine with long-wavelength light resulted in selective cleavage of the C–N bond. On the other hand, products derived form C–C bond cleavage were obtained when the irradiation was carried out with short-wavelength light. On the basis of molecular orbital (MO) calculations using the intermediate neglect of differential overlap/screened approximation (INDO/S) method, it was proposed that C–N bond cleavage occurs from an excited triplet state having an electronic character of a localized π–π^*-excitation on the naphthyl moiety.

1.01.9.3 Reaction of 2*H*-Azirines with Nucleophiles

A very common reaction of 2*H*-azirines involves the addition of various nucleophiles to the ring carbon atom to produce substituted aziridines, which may undergo further reaction by a subsequent ring opening. For example, allylindium reagents react with 2*H*-azirines of type **772** to give allyl aziridines **773** in good yield. A *cis*-allylation with respect to the substituent on the ring was realized with 2*H*-azirines bearing a hydroxymethyl **772a** or an acetoxymethyl **772b** group due to chelation with the allylindium reagent <2006TL1613)>. In contrast, only *trans*-allylation occurred to give **774** with 2*H*-azirines **772c** substituted with a methyl, phenyl, or ester group owing to steric repulsion (**Scheme 186**).



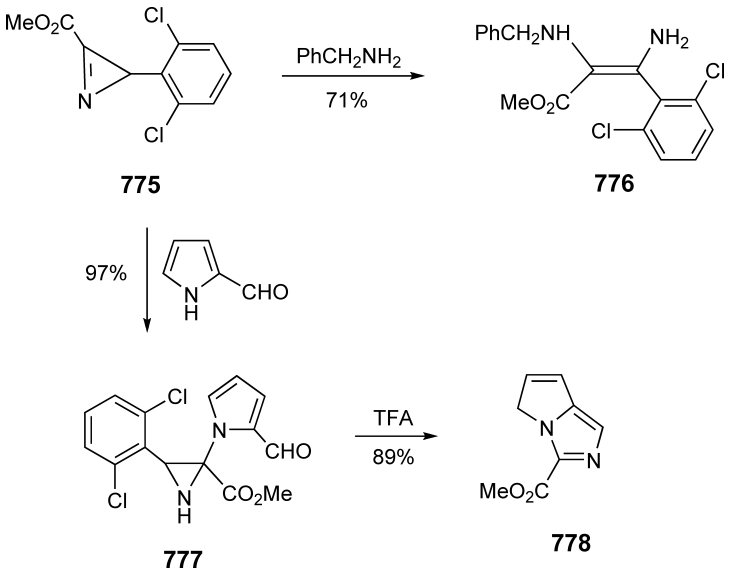
Scheme 186

2*H*-Azirines are more susceptible to nucleophilic attack than other imines as a consequence of the strained nature of the C═N bond. When this ring strain is combined with the presence of an activating group on the carbon atom, nucleophilic addition reactions occur very easily. For example, when methyl 2-aryl-2*H*-azirine-3-carboxylate **775** was used as the substrate, reaction with benzyl amine induced a ring opening by addition of the amino group onto the C═N bond followed by cleavage to provide enediamine **776** <1999J(P1)1305>. The intermediate amino-substituted aziridine adduct could not be isolated with primary or secondary amines since the amino aziridine is easily cleaved. However, when pyrrole-2-carboxaldehyde was used as the nucleophile, it was possible to isolate the pyrroloaziridine **777**. Aziridine **777** was found to undergo a further transformation when treated with TFA at room temperature to give the 5*H*-pyrrolo[1,2-*c*]imidazole **778** in good yield (**Scheme 187**). A similar reaction occurred with other five-membered aromatic heterocycles <2000TL4991>.

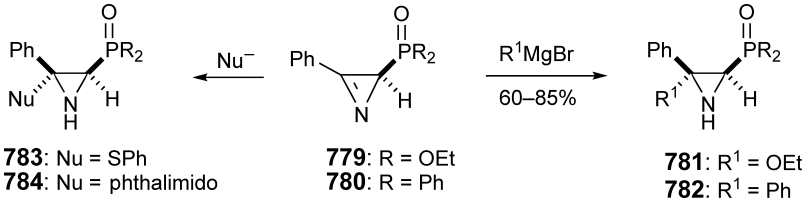
A simple and efficient stereoselective synthesis of aziridine-2-phosphonate **781** and phosphine oxide **782** was achieved by diastereoselective addition of Grignard reagents to 2*H*-azirine phosphonate **779** and phosphine oxide **780**. Addition of benzenethiol and heterocyclic amines proceeded in an analogous manner to yield functionalized aziridines **783** and **784** (**Scheme 188**).

In contrast, treatment of the related 2*H*-azirine-3-methylacrylate **785** with imidazoles and pyrazoles gave 2-aza-1,3-dienes **786** derived from a transient addition product (**Scheme 189**) <1999JOC49>. These dienes are useful in hetero-Diels–Alder reactions with electron-deficient dienophiles.

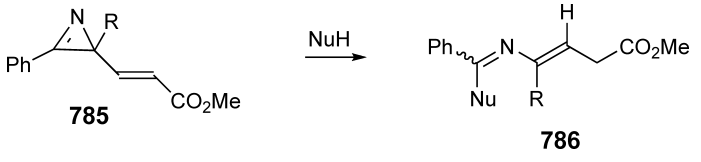
The chiral enriched ethyl 3-methyl-2*H*-azirine-2-carboxylate **787** was found to act as an efficient alkylating agent for the preparation of a variety of five-membered aromatic nitrogen heterocycles **788** (**Scheme 190**) <2003TL6277>.



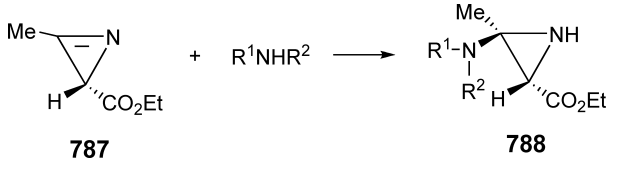
Scheme 187



Scheme 188

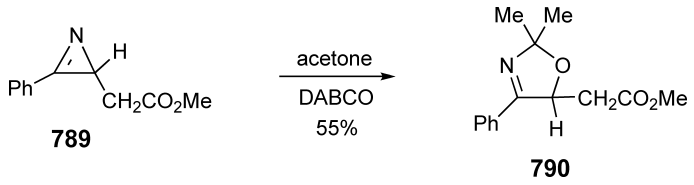


Scheme 189



Scheme 190

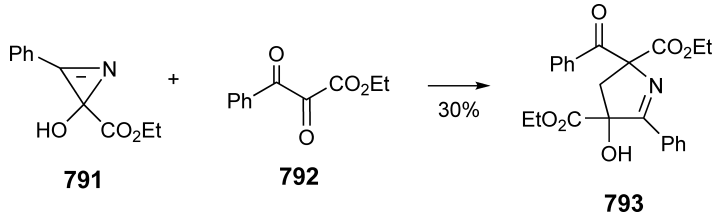
Azirines which have pendant electron-withdrawing functionality undergo an interesting reaction with aldehydes and acetone via a so-called '3-X mode', a reactivity arising from the pushing effect on the 2*H*-azirine ring by the active methylene center. Thus, 2*H*-azirine ester **789** reacts with acetone in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to give the 3-oxazoline **790** (**Scheme 191**) <1996JOC3749>.



Scheme 191

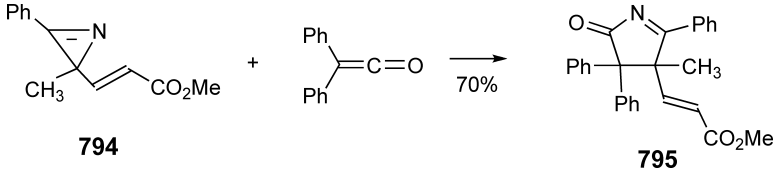
1.01.9.4 Reaction of 2*H*-Azirines with Electrophiles and Metal-Induced Reactions

Although the basicity of the nitrogen atom in the 2*H*-azirine ring is less than in simple aliphatic imines, the imino π-bond can still function as a nucleophilic reagent and react with different electrophilic compounds. For example, the reaction of 2-hydroxy-2*H*-azirine **791** with the dioxo ester **792** gives rise to a 3-oxazoline **793** (**Scheme 192**) <2000TL7217>. The reaction probably involves a nucleophilic attack of the 2*H*-azirine onto the reactive carbonyl oxygen of **792** followed by ring opening and a subsequent intramolecular nucleophilic addition with formation of the five-membered heterocycle.



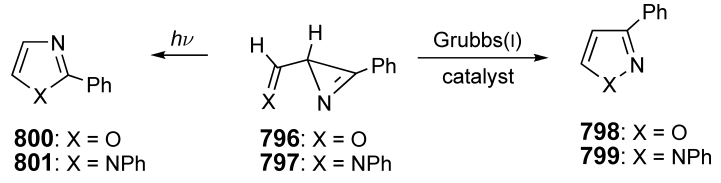
Scheme 192

The reaction of simple 2*H*-azirines with heterocumulenes proceeds to give a wide range of heterocyclic adducts. For example, treating 2*H*-azirine-3-methylacrylate **794** with diphenylketene afforded 5-pyrrolin-2-one **795** in 70% yield (**Scheme 193**) <1997T7089>. A related reaction occurred using *N*-sulfonylimines to give 1,2,5-thiodiazoles <1996J(P1)1629>.



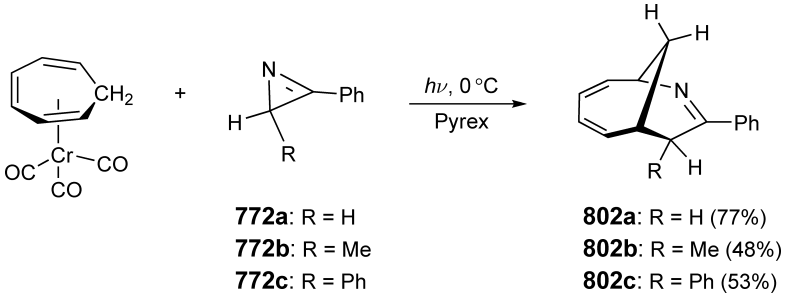
Scheme 193

By comparison with the extensive studies carried out on the thermal and photochemical behavior of the 2*H*-azirine ring system, its behavior toward organometallic reagents has been relatively unexplored. Reaction of 2*H*-azirines **796** and **797** with the commonly employed Grubbs(I) catalyst was found to induce a clean rearrangement, producing isoxazole **798** and pyrazole **799** in good yield. These results stand in marked contrast to the photochemical behavior of **796** and **797**, which afforded 2-phenyloxazole **800** and 1,2-diphenylimidazole **801** as the exclusive products <2004TL5991>. The isolation of isoxazole **798** and pyrazole **799** by use of the Grubbs(I) catalyst clearly indicates that these transition metal-catalyzed transformations occur by C–N bond fragmentation as opposed to C–C bond cleavage which occurs photochemically (**Scheme 194**).



Scheme 194

UV irradiation of tricarbonyl(cycloheptatriene)chromium(0) and 2-phenyl-2*H*-azirines of type **772** through Pyrex at 0 °C leads to 7-aza-8-phenylbicyclo[4.3.1]deca-2,4,7-trienes **802** via a novel [6+3] cycloaddition of the azirine to the cycloheptatriene ring <1995TL1577>. The bicyclic product **802** arises from addition of the 2*H*-azirine C=N bond across the 1- and 6-carbons of the cycloheptatriene ring. The observed N–C bond scission is somewhat surprising since 2*H*-azirines generally undergo C–C bond cleavage under photochemical conditions. Nevertheless, metal- and thermally mediated reactions of azirines cleave the C–N bond, and it was suggested by the authors that the role of light in the reaction is not to open the 2*H*-azirine ring but rather to open a coordination site at the metal by CO ejection or ring slippage. Coordination of the 2*H*-azirine nitrogen to this site then facilitates cleavage of the C–N bond and coupling of the coordinated groups in a [6+3] fashion. Noteworthy is that **772b** and **772c** gave single isomers of the 9-substituted species **802b** and **802c**. This stereocontrol may be due to the steric bulk of the metal and its ancillary ligands, which force the 2*H*-azirine to coordinate in a particular orientation prior to bond formation (**Scheme 195**).

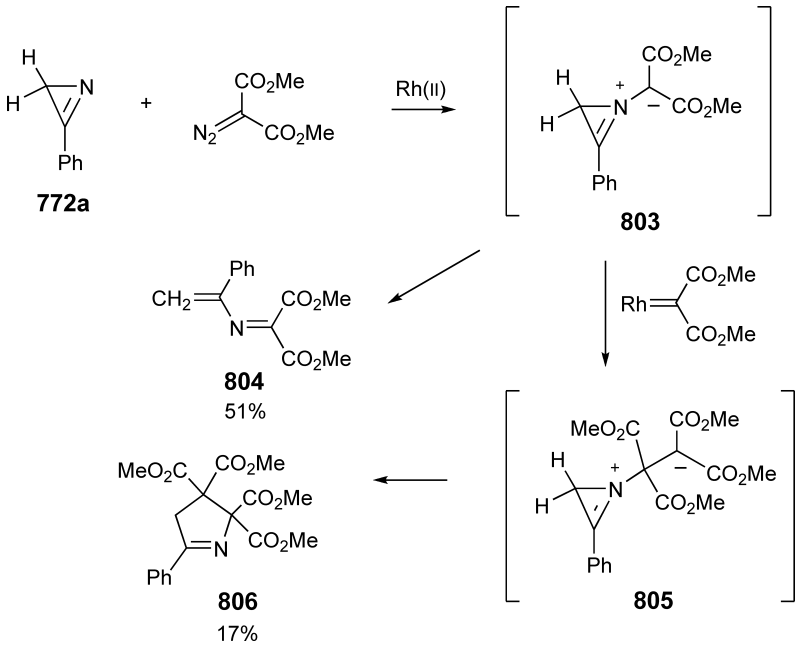


772a: R = H
772b: R = Me
772c: R = Ph

802a: R = H (77%)
802b: R = Me (48%)
802c: R = Ph (53%)

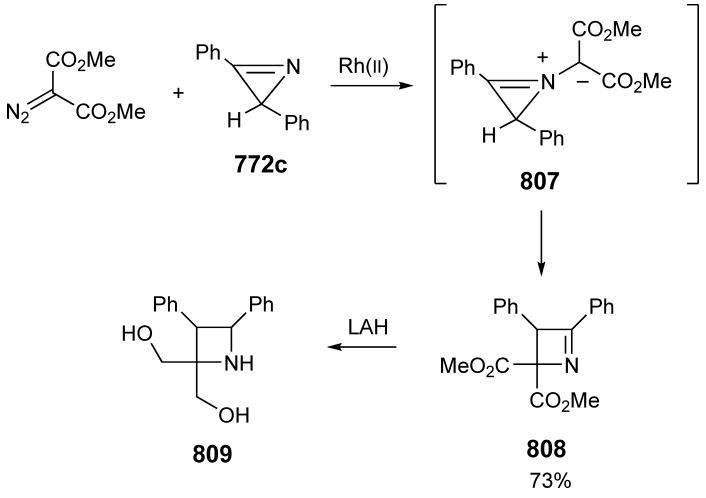
Scheme 195

The thermocatalytic Rh(II) decomposition of diazo malonate in the presence of 3-aryl-2*H*-azirine **772a** was proposed to give rise to an azirinium ylide **803** <2004TL6003>. This reactive ylide is preferentially transformed into 2-azabuta-1,3-diene derivative **804** or, with excess diazo compound, via reaction with the Rh-carbenoid, forms the 3,4-dihydro-2*H*-pyrrole derivative **806** via intermediate **805** (**Scheme 196**).



Scheme 196

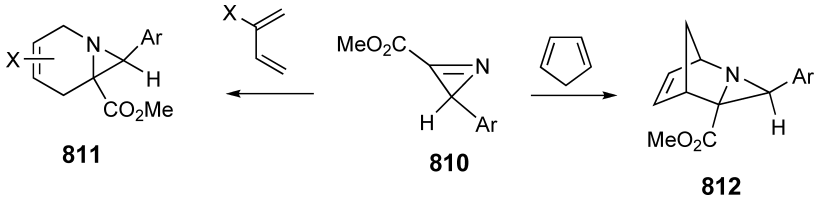
Interestingly, the reaction of the more heavily substituted diphenyl 2*H*-azirine **772c** afforded azetine **808** in 73% yield when it was allowed to react with diazo malonate in the presence of $Rh_2(OAc)_4$. The structure of azetine **808** was established by reduction to diol **809** under the action of $LiAlH_4$ (**Scheme 197**). It would appear as though the reactivity of the initially formed azirinium ylide is dependent on the degree of substitution about the 2*H*-azirine ring.



Scheme 197

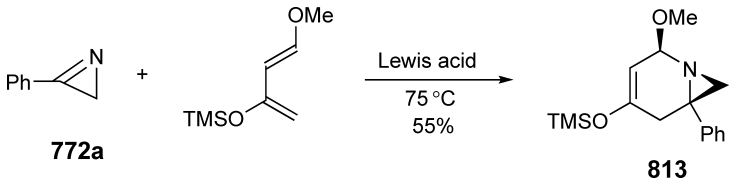
1.01.9.5 2*H*-Azirines as Dienophiles or Dipolarophiles in Cycloaddition Reactions

The strained, electron-rich carbon–nitrogen double bond present in the 2*H*-azirine ring is more reactive than the corresponding double bond in an imine and, while 2*H*-azirines participate in reverse electron-demand Diels–Alder reactions <1996CHEC-II(1A)1>, there are only a few publications describing the normal electron-demand Diels–Alder reactions of 2*H*-azirines. Methyl 2-aryl-2*H*-azirine-3-carboxylates **810** are good dienophiles and they readily react with a variety of dienes to give bicyclic products such as **811** and **812** by cycloaddition across the C–N double bond (**Scheme 198**). The cycloadditions are *endo*-selective and the dienophile approach takes place from the less-hindered face of the 2*H*-azirine <1997S271, 1998TL7579, 1998J(P1)299>. The Diels–Alder reactions of a chiral ester of 2*H*-azirine-3-carboxylic acid with cyclopentadiene was observed to be highly diastereoselective <1999J(P1)1399>.



Scheme 198

Activation by Lewis acids of 3-alkyl- and 3-phenyl-2*H* azirines also promotes their participation in hetero-Diels–Alder reactions with a variety of dienes. This methodology circumvents the previous requirement of needing an electron-withdrawing carboxyl moiety at the 3-position of the 2*H*-azirine ring <2001TL9289>. Thus the reaction of 2*H*-azirine **772a** with Danishefsky's diene gave the *endo*-cycloadduct **813** when the reaction was carried out using 0.3 equiv of a Lewis acid (i.e., $ZnCl_2$, $YbCl_3$, $CuCl_2$) at 75 °C (**Scheme 199**). Several other, less-activated dienes could also be used for the reaction.

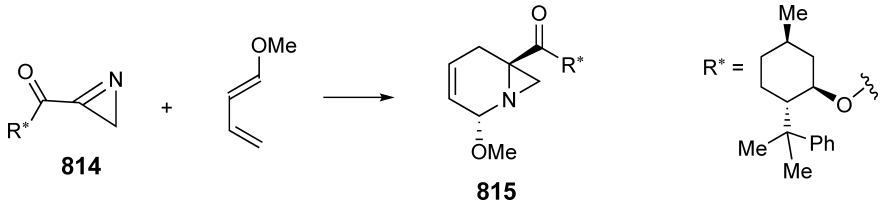


772a **813**

Scheme 199

Highly diastereoselective Lewis acid-mediated aza-Diels–Alder reactions of chiral auxiliary derivatized 2*H*-azirines have been studied <2002T5983, 2003JOC9958, 2003CC1150>. The cycloaddition proceeded with high diastereoselectivity (97% de), with the absolute stereochemistry of the major product confirmed by X-ray crystallography. Without the presence of a Lewis acid, no diastereoselectivity was obtained at room temperature.

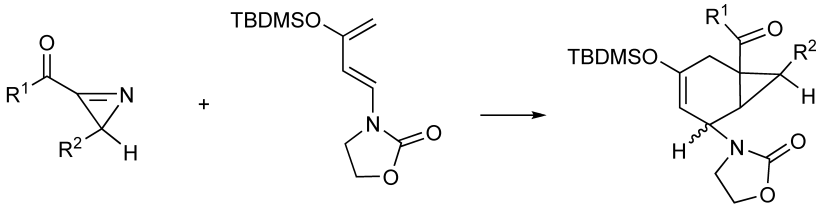
The dramatic effect observed on the reaction diastereoselectivity upon addition of a Lewis acid to 2*H*-azirine **814** could be explained by a bidentate coordination of the Lewis acid to the azirine nitrogen and the carbonyl group. This chelation would lead to hindered rotation around the azirine-carbonyl single bond and thus greater stereoselectivity. The increased reaction rate also indicates coordination of the Lewis acids to the 2*H*-azirine which leads to a lowering of the LUMO energy level and thus an increased reactivity toward the electron-rich diene (**Scheme 200**).



814 **815**

Scheme 200

2*H*-Azirines are excellent partners in aza-Diels–Alder reactions that occur at room temperature when the C=N bond is activated with a conjugated oxo, alkoxycarbonyl, or heteroaromatic group <2005S555>. For example, 3-(3-*tert*-butyldimethylsilyloxy)buta-1,3-dienyl)oxazolidin-2-one **817** reacted with several electrophilic 2*H*-azirines of type **816** to furnish the expected [4+2] cycloadducts **818** in moderate to good yield <2006T3095>. The chiral oxazolidinone **817** was also allowed to react with the same electrophilic 2*H*-azirines but showed no diastereoselectivity for the cycloaddition. 2*H*-Azirine **816b** underwent smooth [4+2] cycloaddition with furan, diphenylisobenzofuran <2001J(P1)2969>, and several electron-rich 2-azadienes (**Scheme 201**) <2003TL5079>. All of the [4+2] cycloaddition reactions were found to be *endo* and regioselective with the 2*H*-azirine being added from its less-hindered face.

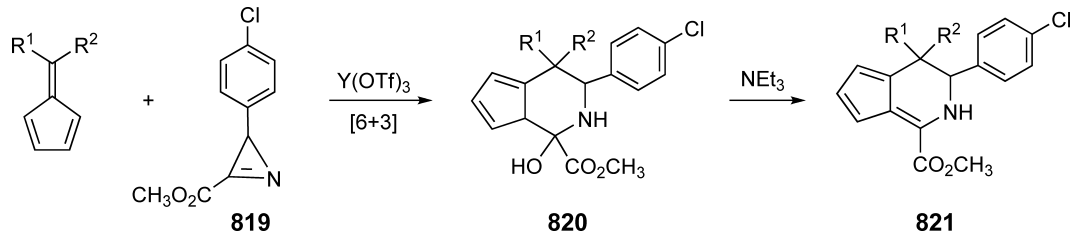


816a: R^1 = Ph; R^2 = Et
816b: R^1 = OMe; R^2 = 2,6-Cl_2Ph

817 **818**

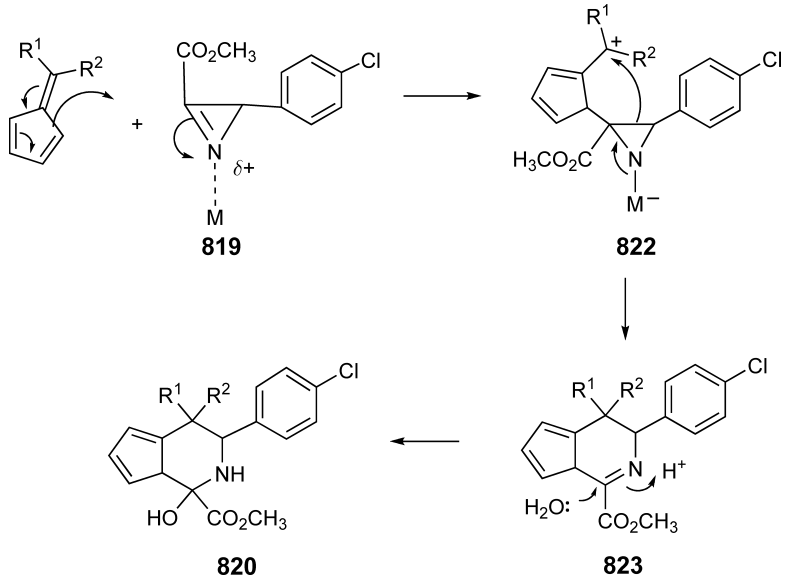
Scheme 201

2*H*-Azirine **819** also undergoes reaction with various fulvenes in THF at 25 °C to afford the corresponding [2]pyridine **820** in 19% yield as the only isolable product. The yield of the [6+3] cycloadduct **820** improved to 83% in the presence of 20 mol% $Y(OTf)_3$ in THF <2004TL1663>. [2]Pyrindine **820** proved to be unstable and was gradually converted to **821** after standing for a few days in the refrigerator (**Scheme 202**).



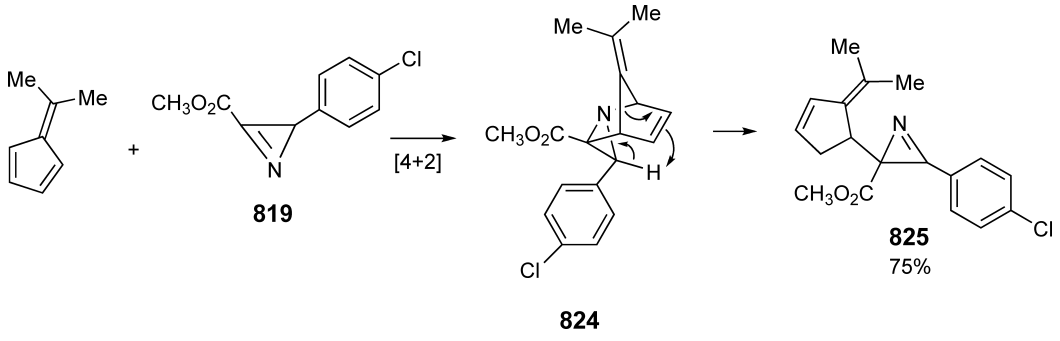
Scheme 202

The formation of **820** was rationalized by a stepwise mechanism. The initial addition of the fulvene to the activated 2*H*-azirine generates the zwitterionic intermediate **822** which then cyclizes to [2]pyrindine **820** via intermediate **823** (**Scheme 203**).



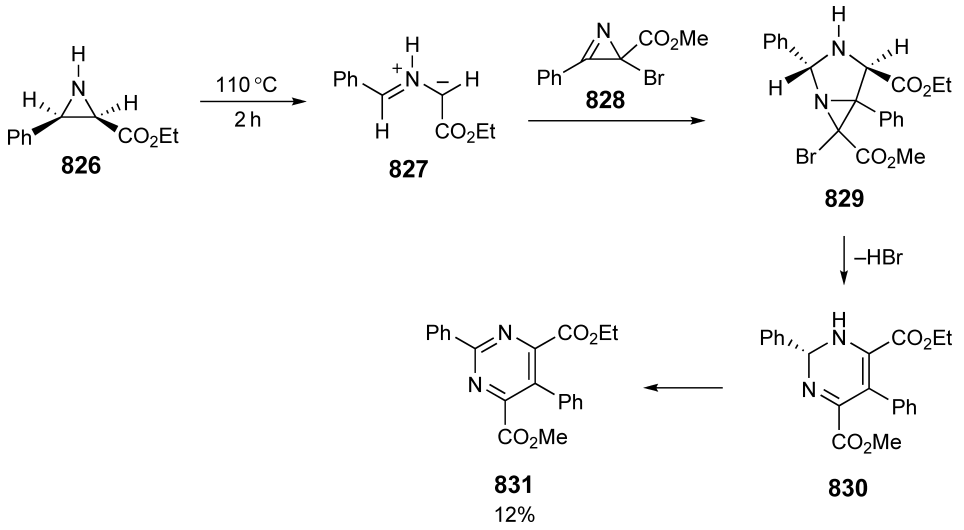
Scheme 203

Interestingly, the reaction of dimethyl fulvene (R = Me) with 2*H*-azirine **819** in an ultrasonic bath (neat) yielded the alkylation product **825**. The structure of **825** was unambiguously assigned by single crystal X-ray structure. A possible mechanism to account for the formation of **825** involves an initial [4+2] cycloaddition followed by a subsequent rearrangement of the initially formed Diels–Alder cycloadduct **824** (**Scheme 204**).



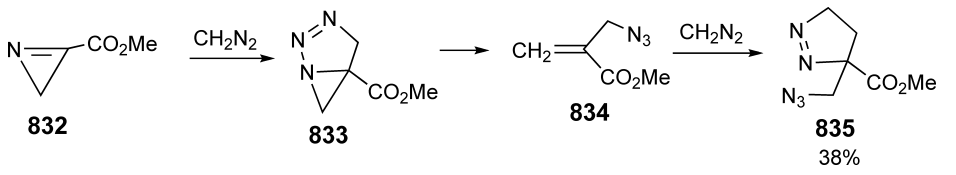
Scheme 204

The 2*H*-azirine ring can also be used as a dipolarophile. The formation of pyrimidine **831** from the reaction of aziridine **826** with 2*H*-azirine **828** in toluene was rationalized by a 1,3-dipolar cycloaddition across the 2*H*-azirine π-bond. Thus, thermal ring opening of aziridine **826** gave the expected azomethine ylide dipole **827** which reacted by way of a [3+2] cycloaddition with 2*H*-azirine **828** to afford cycloadduct **829**. This transient intermediate underwent a subsequent ring-opening reaction with elimination of HBr, leading to dihydropyrimidine **830**, and this was followed by aromatization to give the observed product **831** (**Scheme 205**) <2003TL6313>.



Scheme 205

The reaction of 2*H*-azirine-3-carboxylate **835** with diazomethane occurs to produce a 4,5-dihydro-3*H*-pyrazole derivative **835**. This reaction represents an interesting example of the imino group acting as a 2π-component in a 1,3-dipolar cycloaddition reaction <2003TL6319>. The process seemingly involves the reaction of 2*H*-azirine **832** with diazomethane to give cycloadduct **833** as a transient species which then undergoes a subsequent rearrangement to generate allyl azide **834**. This compound participates in a second 1,3-dipolar cycloaddition with diazomethane to give **835** (**Scheme 206**).



Scheme 206

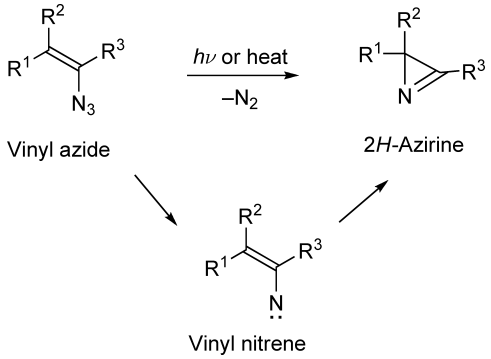
1.01.10 Synthesis of 2*H*-Azirines

1.01.10.1 Photo- or Thermal Extrusion of Nitrogen

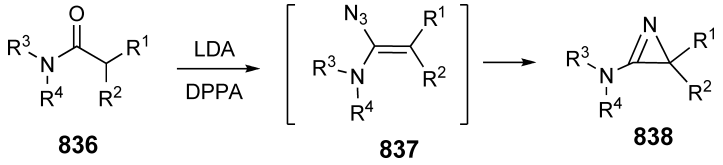
A number of synthetic methods are available for forming 2*H*-azirines such as intramolecular rearrangements of N-functionalized imines, vinyl azides, isoxazoles, and oxazaphospholes. 2*H*-Azirines have also been prepared by bimolecular reactions between nitriles and carbenes or nitrenes and acetylenes. A well-known method for preparing 2*H*-azirines involves the photo- or thermal extrusion of nitrogen from vinyl azides <2003TL5339>. This rearrangement can take place in a concerted manner or via a vinyl nitrene intermediate. An efficient and environmentally friendly method for preparing 2*H*-azirines was achieved by microwave irradiation of vinyl azides in solvent-free conditions (**Scheme 207**) <2003TL6763>.

The vinyl azide method has been employed to prepare heterospirocyclic 3-amino-2*H*-azirines, which represent useful synthons for heterocyclic amino acids <1997HCA1528>. Diphenyl phosphorazidate (DPPA) was used as the azide

source and, by substitution of the oxygen atom of amide enolates, 3-amino-2*H*-azirines **838** were obtained in 'one pot' and high yield <1995HCA1983>. For the synthesis of optically active 3-amino-2*H*-azirines, a modification of this approach with a chiral substituent at the amino group of the thioamide has been used (**Scheme 208**) <1996HCA1903>.

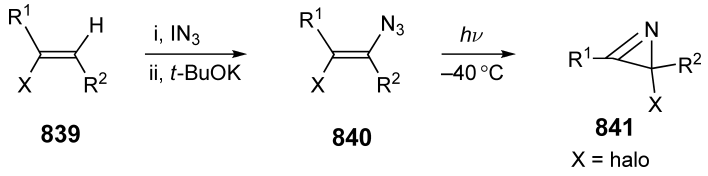


Scheme 207



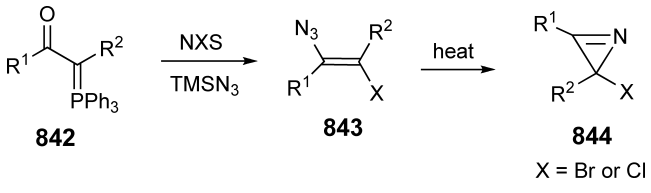
Scheme 208

The reaction of iodine azide with haloalkenes **839** followed by elimination of hydrogen halide by potassium *tert*-butoxide gives the corresponding halovinyl azides **840**, which can be converted into haloazirines **841** by photolysis at −40 °C (**Scheme 209**) <2004COS275>.



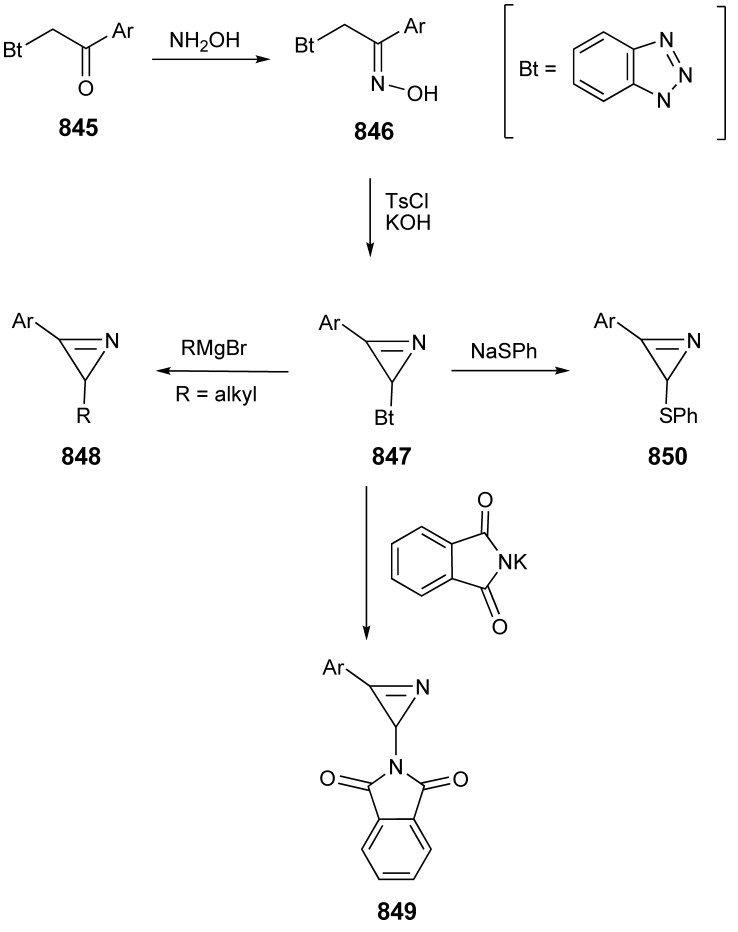
Scheme 209

An alternate route to the same halo 2*H*-azirine system starts from α-oxophosphorus ylides **842**. These ylides react with chlorine, bromine, and electrophilic halogen donor reagents in the presence of nucleophiles and give substituted alkenes of type **843** by elimination of triphenylphosphine oxide. When the reaction of **842** was carried out with an *N*-halosuccinimide in the presence of azidotrimethylsilane, haloazidoalkenes **843** were obtained in good yield (Y = N_3). These vinyl azides were easily converted into the corresponding 2-halo-2*H*-azirines **844** upon heating in heptane for 2–3 h (**Scheme 210**) <1999TL789, 2000TL7217, 2001T6203>.



Scheme 210

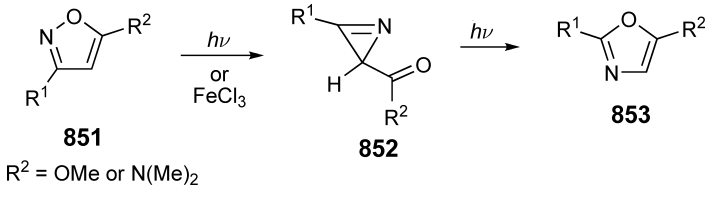
2-(Benzotriazol-1-yl)-2*H*-azirines **847**, obtained by treatment of oximes **846** with tosylchloride and aqueous KOH, were reacted with benzylmagnesium bromide or 4-methylbenzylmagnesium bromide in the presence of zinc chloride and gave 2-benzyl-2*H*-azirines **848**. Potassium phthalimide and the sodium salt of benzenethiol converted the 2-(benzotriazol-1-yl)-2*H*-azirines **847** into novel 2*H*-azirines **849** and **850** (**Scheme 211**) <2003JOC9105>.



Scheme 211

1.01.10.2 Ring Contraction of Isoxazoles

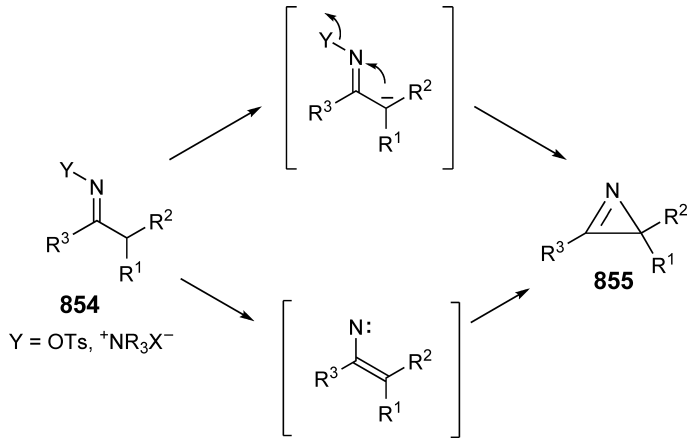
Thermal or photochemical treatment of isoxazoles **851** has been found to result in a ring-contraction reaction to produce acyl 2*H*-azirines **852**, which sometimes rearrange to form other heterocycles like oxazoles **853**. This ring-contraction reaction can also be promoted by iron(II) catalysts. Thus, 5-alkoxy- and 5-aminoisoxazoles isomerize to 2*H*-azirine-2-carboxylic esters and 2*H*-azirine-2-carboxamides, respectively, in nearly quantitative yield by reaction with catalytic $FeCl_2$ (**Scheme 212**) <1997T10911>.



Scheme 212

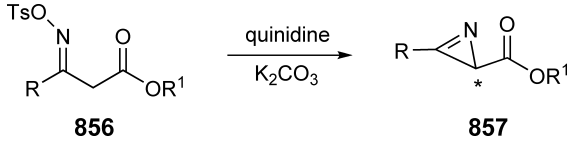
1.01.10.3 Neber Rearrangement of Oxime Sulfonates

Another significant preparative pathway to the 2*H*-azirine system is the Neber rearrangement of oxime sulfonates. The presence of strong electron-withdrawing groups in the α-position to the oxime increases the acidity of those protons, and thus favors the cycloelimination reaction under mild conditions. The Neber reaction occurs either through an internal concerted nucleophilic displacement or via a vinyl nitrene (**Scheme 213**) <2001EJO2401>.



Scheme 213

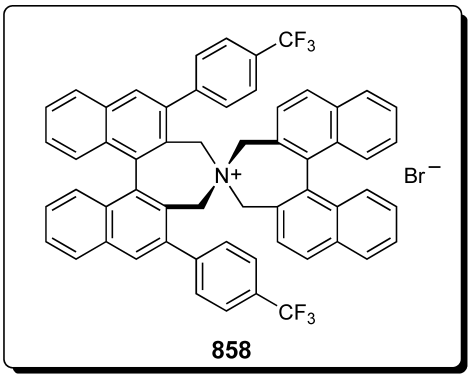
2*H*-Azirines can be prepared in optically enriched form by the asymmetric Neber reaction mediated by *Cinchoma* alkaloids. Thus, ketoxime tosylates **856**, derived from 3-oxocarboxylic esters, are converted to the azirine carboxylic esters **857** in the presence of a large excess of potassium carbonate and a catalytic amount of quinidine. The asymmetric bias is believed to be conferred on the substrate by strong hydrogen bonding via the catalyst hydroxyl group <1996JA8491>. A similar strategy was used for the preparation of alkyl- and aryl-substituted 2*H*-azirines with a phosphonate group in the 2-position of the ring (**Scheme 214**) <2000JOC3213, 2000TL5363, 1998T599>.



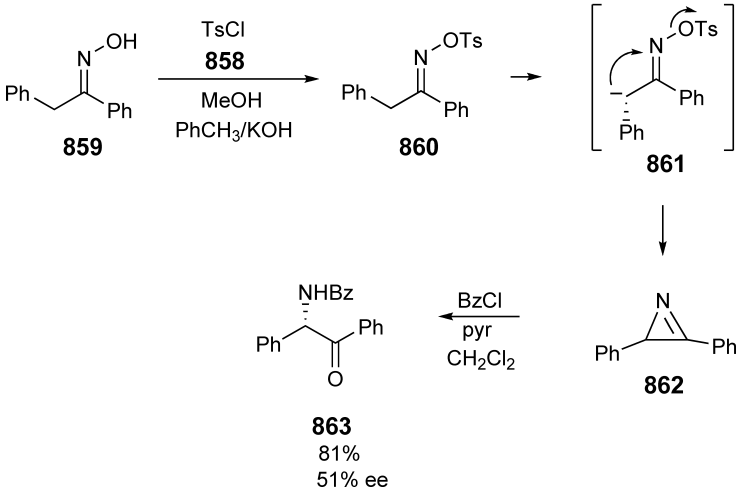
Scheme 214

The Neber route has been noted to be mildly influenced by the introduction of chiral auxiliaries. Thus, rearrangement of the tosyl oxime **860** (formed *in situ* from the oxime **859**) in the presence of catalytic amounts of the chiral quaternary ammonium bromide **858** led to the formation of enantiomerically enriched amino ketone **863**, which is presumed to arise from the preferential formation of the intermediate 2*H*-azirine **862**. Association of the cationic chiral auxiliary with an anionic intermediate (i.e, **861**) has been invoked to rationalize the stereochemical outcome (**Scheme 215**) <2002JA7640>.

Preferential chirality can also be imposed on the sp^2 carbon of the 2*H*-azirine through an asymmetric transfer hydrogenation protocol. Thus, 2*H*-azirine **865** was converted to the scalemic aziridine **866** in 83% yield and 72% ee in the presence of a ruthenium catalyst and the chiral auxiliary **864** in an isopropanol medium (**Scheme 216**) <2002CC1752>.



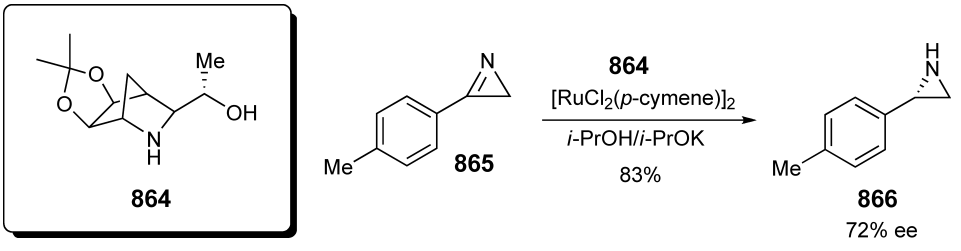
858



859 860 861 862 863

81%
51% ee

Scheme 215



864 865 866

72% ee

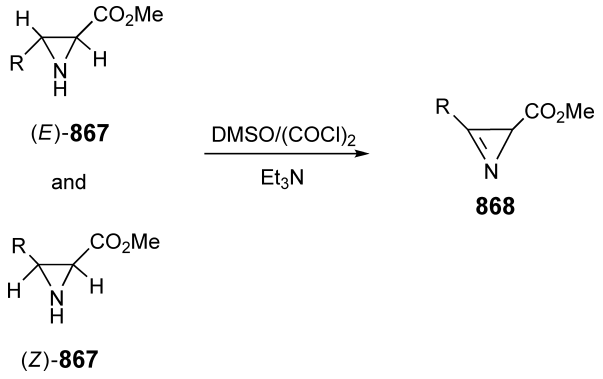
Scheme 216

1.01.10.4 Elimination from *N*-Sulfinylaziridines

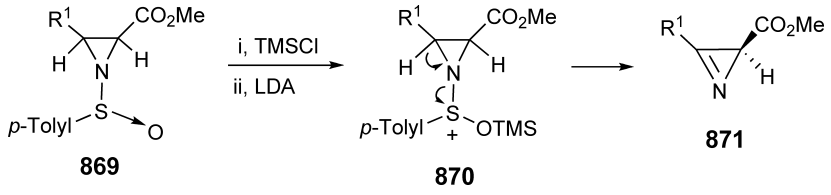
3-Alkyl-2*H*-aziridine-2-carboxylates **867** have been oxidized with the Swern reagent to afford 2*H*-azirine-2-carboxylates <1995TL4665>. Oxidation of either the (*Z*)- or the (*E*)- isomers of **867** provides the same 2*H*-azirine-2-carboxylate **868**, where the integrity of the stereogenic center at C-2 is retained. This regioselectivity results from the unexpected removal of the apparently less acidic C-3 proton during the base-induced *syn*-elimination of the *N*-dimethylsulfonium intermediate (**Scheme 217**).

The closely related 2*H*-azirine-2-carboxylate esters **871** have been prepared in enantiomerically pure form via the base-induced elimination of sulfenic acid from nonracemic *N*-sulfinylaziridine 2-carboxylate esters **869** <1997JOC3796,

1999JOC8929>. For steric reasons, the *N*-sulfinylaziridine invertomers likely adopt structure **870** in which the bulky *p*-toluenesulfinyl group is *anti* to the aziridine ring substituents (**Scheme 218**). This *syn*-periplanar arrangement of leaving groups results in a *syn*-elimination of sulfenic acid to afford 2*H*-azirine **871**.

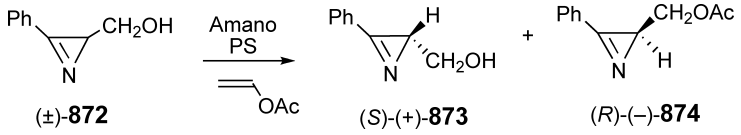


Scheme 217



Scheme 218

Finally, chemoenzymatic synthesis has been used for the preparation of entiomerically pure 2*H*-azirines. Thus, (*S*)-(+)-phenyl-2*H*-azirine-2-methanol **873** and its (*R*)-(−)-acetate **874** were prepared by a lipase-catalyzed kinetic resolution of the racemic 2*H*-azirinemethanol **872**. The reaction was carried out at very low temperature (−40 °C) and therefore enhanced the enantioselectivity (**Scheme 219**) <1997JOC4906>.



Scheme 219

1.01.11 Important Compunds and Applications

Monocyclic aziridines and 2*H*-azirines have found broad application in the synthesis of complex natural products. The facility with which these small ring nitrogen-containing compounds can be converted to important pharmaceutical products under mild conditions with wide functional group compatibility makes these molecules quite useful for heterocyclic chemistry.

1.01.12 Conclusion

This chapter reviews the chemical literature of monocyclic aziridines and 2*H*-azirines from 1995 through 2007. It reveals that aziridines are well-behaved carbon electrophiles capable of reacting with various nucleophiles. The ability of aziridines to undergo regioselective ring-opening reactions contributes largely to their synthetic value.

In ring-opening reactions, it is common either to perform the reactions employing Lewis acid catalysis or to activate the aziridine by substitution on the nitrogen, thus increasing the ability of the nitrogen atom to function as a leaving group. Interesting advances have also been made in the area of ring opening by carbon-centered nucleophiles, an area of obvious practical impact. The same ring strain that lends aziridines reactivity toward nucleophiles also makes them prone to ring-opening isomerizations and rearrangements which can be used for the synthesis of interesting heterocyclic structures. The versatile aziridine functionality can be used in radical-based reactions, [3+2] cycloaddition chemistry, [3+3] annelations, and organolithium-mediated transformations. The chemistry of the related unsaturated 2*H*-azirine system is also quite versatile as a consequence of its high ring strain, reactive π-bond, and its ability to undergo regioselective ring-cleavage reactions. 2*H*-Azirines not only are capable of acting as nucleophiles and electrophiles in organic reactions, but can also act as dienophiles and dipolarophiles in cycloaddition chemistry. Thus, 2*H*-azirines represent very useful precursors for the synthesis of a variety of nitrogen-containing ring systems.

Further Developments

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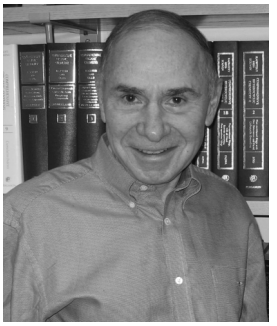
Biographical Sketch



Albert Padwa was born in New York City. He received both his B.A. and Ph.D. degrees from Columbia University. After an NSF postdoctoral position at the University of Wisconsin, he was appointed Assistant Professor of Chemistry at the Ohio State University in 1963. He moved to SUNY Buffalo in 1966 as associate professor and was promoted to professor in 1969. Since 1979, he has been the William Patterson Timmie Professor of Chemistry at Emory University. He has held visiting positions at University Claude Bernard, France, University of California at Berkeley, the University of Wurzburg, Germany, Imperial College of Chemistry, UK, and the University of Melbourne, Australia. Professor Padwa has been the recipient of an Alfred P. Sloan Fellowship, John S. Guggenheim Fellowship, Alexander von Humboldt Senior Scientist Award, a Fulbright Hays Scholarship, Senior Award in Heterocyclic Chemistry from the International Society of Heterocyclic Chemists, ACS Arthur C. Cope Scholar Award, and he is the coauthor of more than 650 publications. He served as chairman of the Organic Division of the ACS and as president of the International Society of Heterocyclic Chemistry. He has also served as a member on the editorial boards of the *Journal of the American Chemical Society*, *Journal of Organic Chemistry*, *Organic Letters*, and has been the volume editor of *Comprehensive Heterocyclic Chemistry*, the *Synthesis of Science* (vol. 27), and is currently one of the associate editors of the *Journal of Organic Chemistry*. His research interests include heterocyclic chemistry, dipolar cycloadditions, alkaloid synthesis, tandem transformations, organometallic chemistry, and organic photochemistry.